Aus der Medizinischen Universitätsklinik und Poliklinik I
am Klinikum der Ludwig-Maximilians-Universität München
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“Neue Ansätze zur Risikostratifizierung und Verbesserung der Therapie bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung”

Habilitationsschrift
zur Erlangung der Venia Legendi
für das Fach Innere Medizin
der Medizinischen Fakultät
der Ludwig-Maximilians-Universität zu München

vorgelegt von
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2017

Meiner liebsten Familie

1. Inhaltsverzeichnis

2. Vorwort

In der vorliegenden kumulativen Habilitationsschrift werden neue Ansätze zur Risikostratifizierung und Therapie bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung zusammengefasst. Einleitend werden die aktuellen Strategien zur Risikostratifizierung nach Myokardinfarkt anhand der linksventrikulären Auswurffraktion dargestellt. Des Weiteren wird auf die Rolle des autonomen Nervensystems und neuer Methoden zur nicht-invasiven Testung der autonomen Funktion nach Myokardinfarkt, sowie bei struktureller Herzerkrankung eingegangen. Am Ende werden neue Ansätze zur Verbesserung der Therapie bei Patienten mit ischämischer Kardiomyopathie evaluiert und diskutiert.

Auf Grundlage von 10 Originalarbeiten (5 Erst-, 2 Letzt-, und 3 Co-Autorenschaften), 2 Übersichtsarbeiten (2 Erstautorenschaften) und eines Leitartikels (Erstautorenschaft) werden die Ergebnisse aus verschiedenen klinischen Studien im Hinblick auf die Risikostratifizierung und Therapie bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung dargestellt. Methodische Einzelheiten und Resultate sowie Abbildungen der jeweiligen Arbeiten finden sich detailliert in den jeweiligen Originalarbeiten (siehe Anhang). Eine Auswahl von Abbildungen im Text soll zentrale Aussagen den Originalarbeiten beispielhaft illustrieren und der Verdeutlichung wichtiger Diskussionspunkte dienen.

Aus Gründen der Übersichtlichkeit wird die zitierte Literatur in **numerischer** Reihenfolge im Literaturverzeichnis aufgeführt. Die eigenen Veröffentlichungen (Erst-, Letzt- und Co-Autorenschaften) zum Thema „Neue Ansätze zur Risikostratifizierung und Therapie bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung“ sind in **alphabetischer** Indizierung (A-M) in einem separaten Verzeichnis aufgeführt.

3. Einleitung

Die Prognose von Patienten nach Myokardinfarkt konnte in den letzten Jahrzehnten signifikant verbessert werden. Erreicht wurde dies durch eine Optimierung der Akutversorgung mit sofortiger Revaskularisation des akut verschlossenen Infarktgefäßes[1,2] und durch die Weiterentwicklung der medikamentösen Begleittherapie[3-5]. Dennoch bleibt die Spätmortalität mit etwa 1,5% pro Jahr hoch[6], auch wenn die Patienten optimal therapiert werden. Etwa jeder zweite Todesfall geschieht unter dem Bild des plötzlichen Herztodes, d.h. innerhalb von Sekunden bis Minuten aus scheinbar stabilen Verhältnissen heraus[7]. In über 90% dieser Fälle ist der Herzkreislaufstillstand durch tachykarde Herzrhythmusstörungen, die in Kammerflimmern degenerieren, verursacht.

Randomisierte Studien konnten belegen, dass Hochrisikopatienten nach Myokardinfarkt von einer primärprophylaktischen Implantation eines Defibrillators („implantable cardioverter-defibrillator“, ICD) profitieren[8,9]. Die Identifizierung geeigneter Patienten erfolgt gegenwärtig durch Bestimmung der linksventrikulären Auswurffraktion (LVEF), welche derzeit als Goldstandard in der Risikoprädiktion gilt[10]. Nach den derzeit gültigen Richtlinien sind Patienten mit hochgradig eingeschränkter LVEF (≤35%) Kandidaten für eine primärprophylaktische ICD-Implantation. Die Sensitivität und Spezifität der LVEF in der Risikoprädiktion nach Myokardinfarkt ist allerdings beschränkt. Etwa 70% der Todesfälle ereignen sich in der Patientengruppe mit erhaltener oder nur moderat eingeschränkter Pumpfunktion[11]. In der Patientengruppe mit hochgradig eingeschränkter LVEF, die mit ICD versorgt wird, erhält innerhalb von 5 Jahren nur jeder dritte Patient eine adäquate ICD-Therapie[12]. Die durch die ICD-Therapie reduzierte Rate des plötzlichen Herztodes ist allerdings mit einer Erhöhung der Rate des nicht plötzlichen Herztodes verbunden[13].

Aus diesen Gründen sind neue Verfahren zur Risikostratifizierung von großer klinischer Bedeutung. Experimentelle und klinische Studien belegen, dass die Qualität autonomer Regelungsprozesse des Herzens eine wesentliche und von der LVEF unabhängige prognostische Informationen trägt[14]. Es gibt Evidenz, dass ein Verlust vagaler Aktivität und ein Übermaß sympathischer Aktivität mit einer schlechten Prognose vergesellschaftet sind. Eine direkte Messung autonomer Aktivität am Herzen ist aufgrund der Invasivität als klinische Untersuchungsmethode

nicht möglich. Stattdessen können autonome Steuerungsprozesse indirekt durch Analyse von kardialen Biosignalen charakterisiert werden.

Im Rahmen dieser Habilitationsarbeit sollen primär neue Ansätze zur Risikostratifizierung nach Myokardinfarkt mit Hauptaugenmerk auf Marker des autonomen Tonus untersucht werden. In einem weiteren Schritt sollen diese Methoden bei Patienten mit struktureller Herzerkrankung angewendet werden. Am Ende sollen neue Ansätze zur Verbesserung der Therapie bei Patienten mit ischämischer Kardiomyopathie evaluiert und diskutiert werden.

4. Klassische Analyse der Herzfrequenzvariabilität

Ein seit langer Zeit bekannter diagnostischer Zugang zum autonomen Nervensystem des Herzens besteht in der Analyse der Herzfrequenzvariabilität (heart rate variability – HRV). In diesem Fall fungiert der, sowohl sympathisch, als auch parasympathisch innervierte, Sinusknoten als „Schreiber der autonomen Funktion“. Zur Bestimmung der HRV werden die aufeinanderfolgenden Schlag-zu-Schlag-Abstände (RR-Intervalle) im Sinne einer Zeitreihenanalyse mit mathematischen Methoden analysiert. HRV gilt als Indikator für die Güte der autonomen Funktion. Kleiger und Mitarbeiter konnten erst in der MPIP (multicenter post-infarction project) Studie zeigen, dass eine eingeschränkte HRV mit erhöhter Gesamtmortalität nach akutem Myokardinfarkt vergesellschaftet ist. Dazu bestimmten die Autoren bei 808 Patienten die Standardabweichung aller Normal-zu-Normal-Intervalle (SDNN) über 24-Stunden[15]. Die prognostische Bedeutung dieses vergleichsweise einfachen HRV-Parameters wurde in mehreren prospektiven Kohorten validiert[16,17]. Eine andere Methode um Rückschlüsse auf die anteilsmäßige Beteiligung zugrundeliegender autonomer Regelungsprozesse an der Gesamtvariabilität zu ziehen, bietet die Frequenzanalyse der HRV. Hierbei wird das Zeitsignal der RR-Intervalle in ein Frequenzspektrum umgewandelt und in 4 Bereiche (Banden) aufgeteilt. Bigger und Mitarbeiter haben den prognostischen Wert spektraler HRV-Parameter an 715 Überlebenden eines akuten Myokardinfarktes untersucht. In der multivariablen Analyse war eine reduzierte Power im sogenannten very- (0.0033 – 0.4 Hz) und ultra-(<0.0033 Hz) low Frequenzbereich hochsignifikant mit der Gesamtmortalität assoziiert[18]. Ein Nachteil der herkömmlichen Maßen der HRV-Bestimmung ist, dass es nicht zwischen vagalen und sympathischen Einflüssen unterschieden werden kann. Darüber hinaus ist ein 24-Stunden Langzeit-EKG erforderlich. Angesichts des immer verkürzten Krankenhausaufenthalts stellt aber dieses Erfordernis ein wesentliches Haupthemmnis dar. Im Folgenden sollen neue nicht-invasive Ansätze zur selektiven Erkennung des vagalen Verlustes und der sympathischen Überaktivität aus Langzeit- und Kurzzeit-EKGs eingegangen werden.

5. Neue Ansätze zur Risikostratifizierung bei Postinfarktpatienten

5.1. Herzfrequenzturbulenz

Die Herzfrequenzturbulenz quantifiziert die Baroreflex-vermittelte Kurzzeitoszillation der Herzfrequenz nach spontan einfallenden ventrikulären Extrasystolen (VES)[19]. Physiologisch kommt es nach einer VES zuerst zu einer Herzfrequenzbeschleunigung, gefolgt von einer progredienten Herzfrequenzverlangsamung. Der erste Teil dieser biphasichen Reaktion wird durch den Turbulence Onset (TO) quantifiziert. Der insuffiziente Auswurf der Extrasystole, sowie die nachfolgende kompensatorische Pause führen zu einer Aktivierung der Barorezeptoren, was einen abrupten Abfall des Vagotonus zur Folge hat. Dies ist die Ursache für die unmittelbare Beschleunigung der Herzfrequenz. Der zweite Teil der biphasischen Reaktion (Herfrequenzverlangsamung), der durch den Turbulence Slope (TS) quantifiziert wird entspricht der mit einer Latenzzeit Reaktion des sympathischen Nervensystems auf den Blutdruckabfall. Die HRT ist einer der bestuntersuchten Risikoparameter nach Myokardinfarkt und ist an mehreren prospektiven Kohorten validiert worden[11]. In einer großen Metaanalyse, die 9 prospektive Studien mit insgesamt 9.709 Patienten einbezog, konnte gezeigt werden, dass ein Abschwächen oder ein Fehlen der typischen HRT-Reaktion mit einem 6.2-fachen Mortalitätsrisko assoziiert war (Abb. 1) **A**.

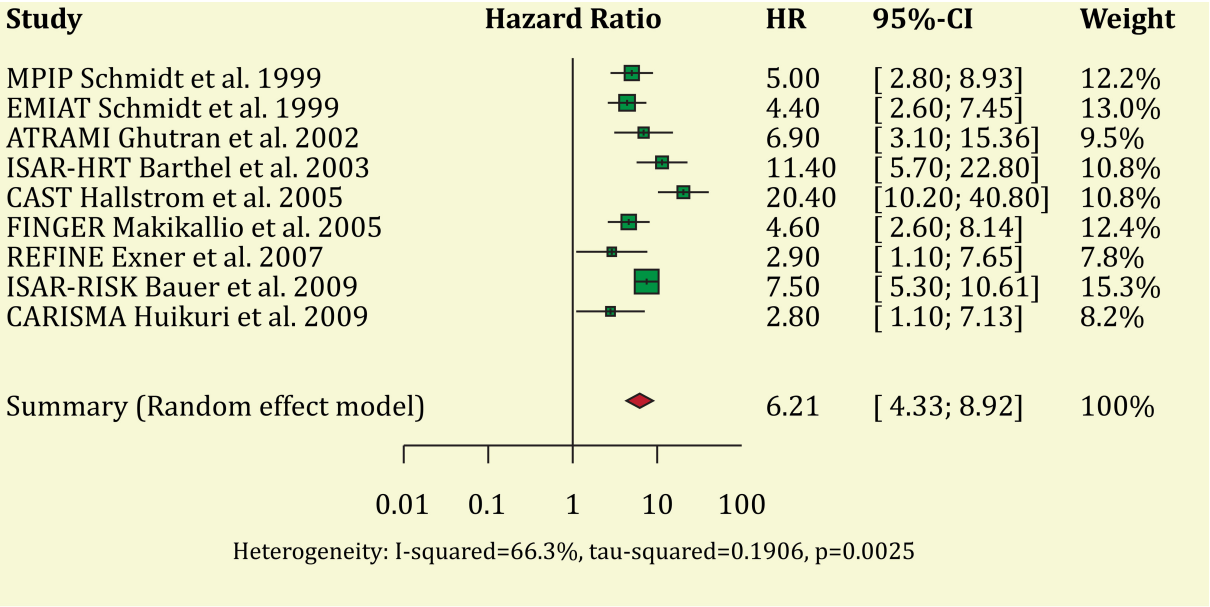

Abb. 1: Metaanalyse des prognostischen Wertes der Herzfrequenzturbulenz für die Prädiktion der Gesamtmortalität. MPIP = Multicenter Post-infarction Program[19], EMIAT = European Myocardial Infarction Amiodarone Trial[19], ATRAMI = Autonomic Tone and Reflexes after Myocardial Infarction[20], ISAR-HRT = Improved Stratification of Autonomic Regulation by means of Heart Rate Turbulence[21], CAST = Cardiac Arrhythmia Suppression Trial[22], FINGER = FINland and GERmany sudden cardiac death trial[22], REFINE = Risk Estimation Following Infarction Non-invasive Evaluation[23], ISAR-RISK = = Improved Stratification of Autonomic Regulation for Risk prediction after myocardial infarction[24], CARISMA = Cardiac Arrhythmias and RIsk Stratification after AMI[25 A].

5.2. Dezelerationskapazität

Die Dezelerationskapazität (deceleration capacity – DC) des Herzens ist ein neues Maß der HRV, das sich in wesentlichen Aspekten von herkömmlichen HRV-Parametern unterscheidet[26,27]. Zur Bestimmung der DC wird die Serie der RR-Intervalle mit Hilfe eines mathematischen Verfahrens (Phase Rectified Signal Averaging – PRSA) in ein neues wesentlich kürzeres Signal transformiert, welches sämtliche Schwingungen des Originalsignals enthält, dabei werden Rauschen und Nicht-Stationaritäten eliminiert[26]. Neben dem Vorteil des signifikant besseren Signal-Rausch-Verhältnisses, besteht zudem eine weitere Besonderheit: Die DC ist ein integrales Maß sämtlicher an Verlangsamungen beteiligter Modulationen der Herzfrequenz und damit ein Maß der vagalen Innervierung des Herzens[26,27]. In einer großen Beobachtungsstudie an insgesamt 2.711 Postinfarktpatienten war DC nicht

nur Standardmaßen der HRV sondern auch der LVEF in der Mortalitätsprädiktion überlegen[24]. Die Bestimmung der DC erforderte bislang die Durchführung eines 24-Stunden Langzeit-EKGs. Angesichts des immer verkürzten Krankenhausaufenthalts stellt dieses Erfordernis ein wesentliches Haupthemmnis dar. Die Berechnung der DC aus Kurzzeit-EKGs wäre deshalb von großem Vorteil und würde die Risikostratifizierung nach Myokardinfarkt im klinischen Alltag ermöglichen. Der prognostische Wert der DC aus Kurzzeit-EKGs nach Myokardinfarkt ist in zwei großen Kohorten mit insgesamt 1.286 Patienten untersucht worden (München-Kohorte, ISAR-Risk,n = 908 und Tübingen-Kohorte, PRD-MI, n = 478) [B]. Der primäre Endpunkt beider Studien war die 3-Jahres-Gesamtmortalität. Der sekundäre Endpunkt war die 3-Jahres-kardiovaskuläre Mortalität. Abb. 2 zeigt repräsentative PRSA-Signale eines Patienten, der den Beobachtungszeitraum überlebt hat (A), sowie eines Patienten, der 9 Wochen nach dem Herzinfarkt verstorben ist (B). Die Amplituden der Periodizitäten sind bei dem verstorbenen Patienten deutlich niedriger als bei dem überlebenden Patienten.

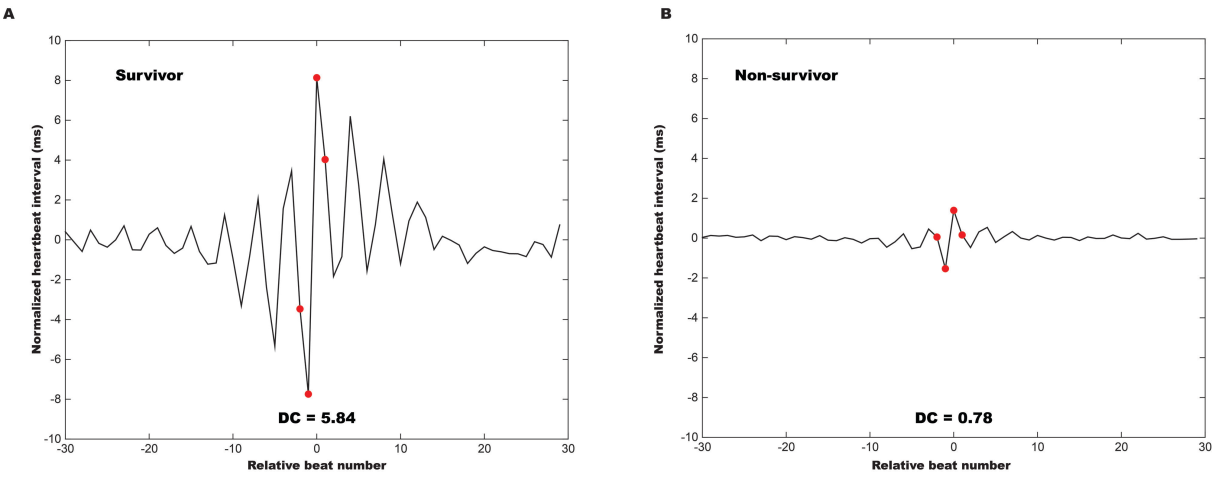

Abb. 2: Repräsentative PRSA-Signale zweier Postinfarkt-Patienten. **(A)** zeigt Dezelerations-bezogene PRSA-Signale eines Patienten der den Beobachtungszeitraum überlebt hat. **(B)** zeigt die Dezelerations-bezogene PRSA-Signale eines Patienten der 9 Wochen nach dem Herzinfarkt verstorben ist. Die Amplituden der Periodizitäten sind bei dem verstorbenen Patienten deutlich niedriger als bei dem überlebenden Patienten [B].

In beiden Kohorten war die eingeschränkte DC der stärkste Prädiktor der 3-Jahres-Mortalität, sowie der 3-Jahres kardiovaskulären Mortalität (Abb. 3) [B]. Multivariable Analysen zeigten, dass der prädiktive Wert der DC unabhängig von anderen etablierten Risikoparametern, wie die LVEF und der GRACE (Global Registry of Acute Coronary Events) Score war (Tab. 1) [B]. Hinzunahme der DC in das multivariable Modell führte zu einem signifikanten Anstieg des C-Indexes und des IDI (integrated discrimination improvenent) Maßes für die Prädiktion der Gesamtmortalität.

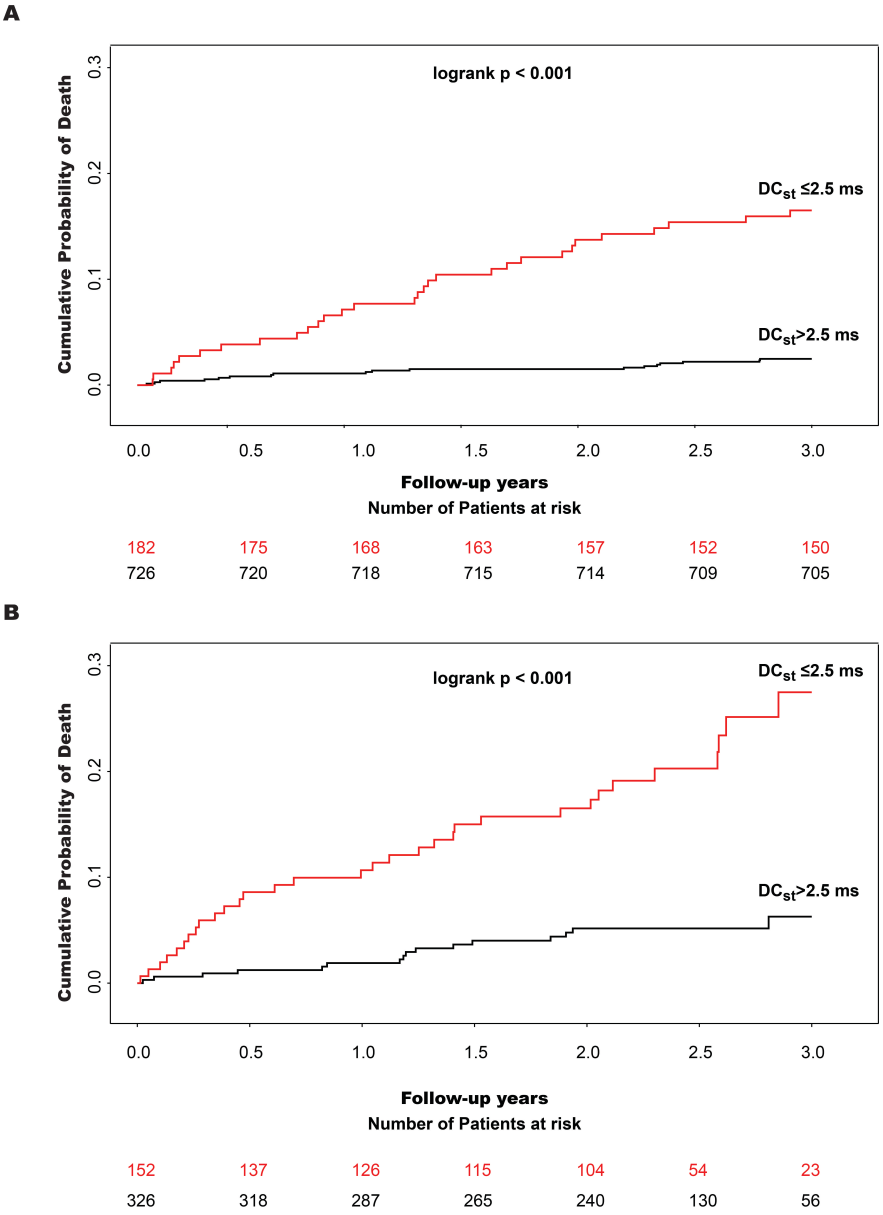

Abb. 3: Kumulative Gesamt- und kardiovasuläre Mortalitätskurven von Postinfarktpatienten in zwei großen prospektiven Kohorten (**A** = ISAR-Risk, n = 908; **B** = PRD-MI, n = 455) stratifiziert nach der Dezelerationskapazität des Herzens [B].

Tab. 1: Uni- und multivariable Cox-Regressionsanalyse für die Prädiktion der 3-Jahres Gesamtmortalität und der 3-Jahres-kardiovaskulären Mortalität bei 908 Postinfarkt-Patienten der ISAR-Risk Studie und bei 478 Patienten der PRD-MI Studie [B].

Munich cohort (ISAR-Risk): All-cause mortality				
Risk variable	**Univariable Cox Regression**		**Multivariable Cox Regression**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
GRACE score >140	4.35 (2.36 – 8.01)	<0.001	1.91 (0.98 – 3.73)	0.059
LVEF ≤35%	5.27 (2.89 – 9.61)	<0.001	2.75 (1.43 – 5.27)	0.002
DC_{st} ≤2.5ms	7.18 (4.00 – 12.87)	<0.001	5.04 (2.68 – 9,49)	<0.001
Munich cohort (ISAR-Risk): Cardiovascular mortality				
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
GRACE score >140	4.00 (1.75 – 9.14)	0.001	1.72 (0.69 – 4.27)	0.245
LVEF ≤35%	6.13 (2.81 – 13.38)	<0.001	3.47 (1.48 – 8.12)	0.004
DC_{st} ≤2.5ms	6.21 (2.88 – 13.37)	<0.001	4.18 (1.81 – 9.68)	<0.001
Tuebingen cohort (PRD-MI): All-cause mortality				
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
GRACE score >140	3.48 (1.89 – 6.42)	<0.001	2.29 (1.20 – 4.37)	0.012
LVEF ≤35%	4.16 (2.35 – 7.37)	<0.001	2.07 (1.11 – 3.86)	0.023
DC_{st} ≤2.5ms	4.57 (2.51 – 8.33)	<0.001	3.19 (1.70 – 6.02)	<0.001
Tuebingen cohort (PRD-MI): Cardiovascular mortality				
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
GRACE score >140	3.79 (1.57 – 9.16)	0.003	2.49 (0.98 – 6.35)	0.056
LVEF ≤35%	4.44 (1.99 – 9.93)	<0.001	2.31 (0.95 – 5.60)	0.065
DC_{st} ≤2.5ms	3.79 (1.66 – 8.67)	0.002	2.51 (1.04 – 6.03)	0.040

DC_{st} = Dezelerationskapazität aus Kurzzeit EKGs, GRACE = Global Registry Acute Coronary Events, LVEF = linksventrikuläre Auswurffraktion

Des Weiteren evaluierten wir den prognostischen Wert der DC aus Kurzzeit-EKGs als Risikoprädiktor in der Notaufnahme. DC war ein sehr starker Prädiktor der 6-Monats-Mortalität bei unselektionierten Patienten (Abb. 4) [C], sowie bei Patienten mit Verdacht auf akutes Koronarsyndrom (Abb. 5) [D].

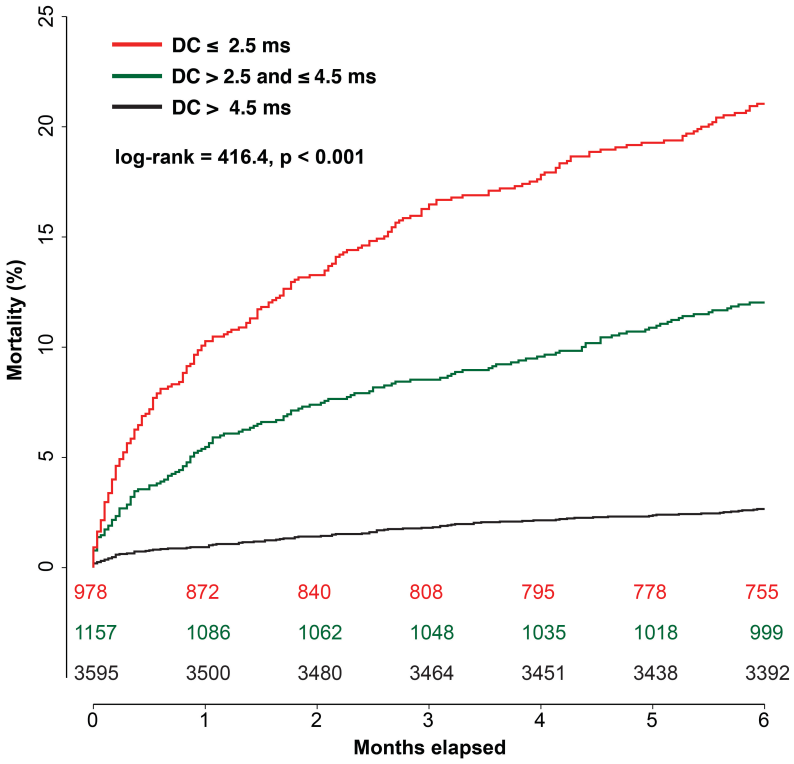

Abb. 4: Kumulative Mortalitätskurven bei unselektionierten Patienten in der Notaufnahme stratifiziert nach der Dezelerationskapazität des Herzens [C].

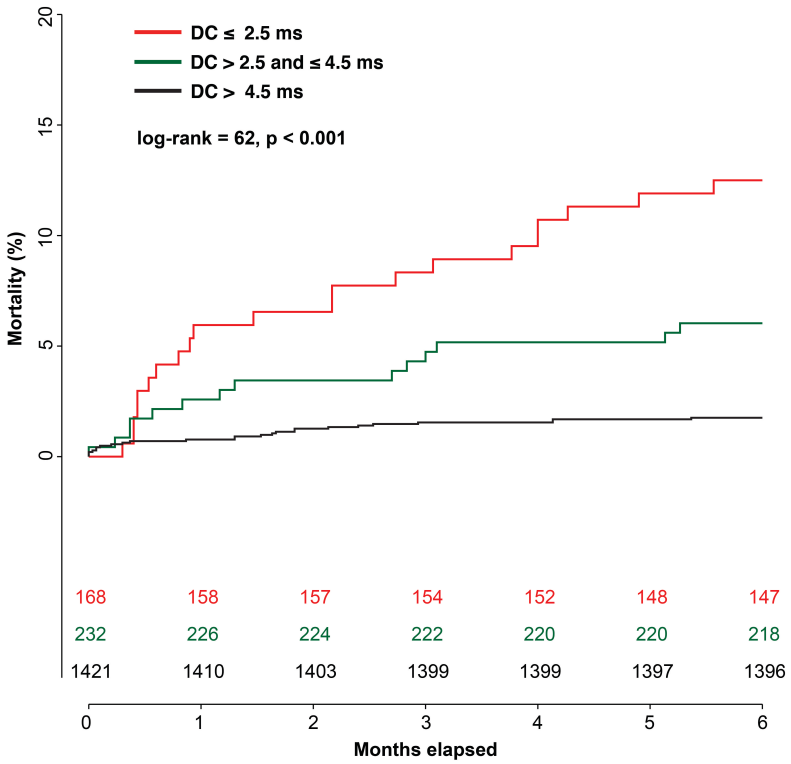

Abb. 5: Kumulative Mortalitätskurven bei Patienten mit Verdacht auf akutes Koronarsyndrom stratifiziert nach der Dezelerationskapazität (DC) des Herzens [D].

5.3. Periodic Repolarization Dynamics (PRD)

5.3.1. Berechnung der PRD

Aus direkten Nervenableitungen ist bekannt, dass sympathische Entladungen am Herzen in sogenannte niederfrequenten „Bursts“ organisiert sind (≤0,1 Hz; entsprechend Zykluslänge >10s)[28]. Mit Hilfe mathematischer Methoden konnte nachgewiesen werden, dass die kardiale Repolarisation in Ruhe niederfrequenten Modulationen unterliegt, welche mit bloßem Auge nicht sichtbar sind [E]. Dieses neue elektrokardiographische Phänomen, das zuerst 2014 erfunden worden ist [E], wird “Periodic Repolarization Dynamics“ (PRD) genannt [E,F,G]. Um die PRD zu bestimmen, ist eine hochaufgelöste EKG-Aufzeichnung erforderlich. Die Untersuchung sollte in den orthogonalen, Frank-Ableitungen (X, Y und Z) über einen Zeitraum von mindestens 20-Minuten erfolgen. Da die Messung auf extrinsische oder intrinsische Störfaktoren empfindlich sein kann, sollte sich der liegende Patient in einer ruhigen Umgebung befinden und spontan atmen. Schematisch erfolgt die PRD-Bestimmung in den folgenden Schritten:

- Im ersten Schritt der Berechnung werden die kartesischen Koordinaten X, Y und Z in eine Zeitfolge von polaren Koordinaten umgewandelt. Der ursprüngliche Vektor wird dabei in zwei Winkel (Elevation und Azimut) und eine Länge zerlegt.
- Als nächstes wird auf Basis der orthogonalen Koordinaten die gewichtete Richtung der Repolarisation definiert. Dafür werden Azimut und Elevation für jeden Zeitpunkt der T-Welle mit der Länge multipliziert. Die Summe aller Produkte wird anschließend mit der Summe aller Längen dividiert. Die dabei entstehenden polaren Winkel werden gewichteter Azimut (*weight-averaged azimuth*, WAA) und gewichtete Elevation (*weight-averaged elevation*, WAE) genannt. Gleichung 1 und Gleichung 2, sowie Abb. 6 und 7 zeigen die Berechnung von WAA und WAE.

$$Weight\ Averaged\ Azimuth\ (WAA) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * Azimuth_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (1)$$

$$Weight\ Averaged\ Elevation\ (WAE) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * Elevation_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (2)$$

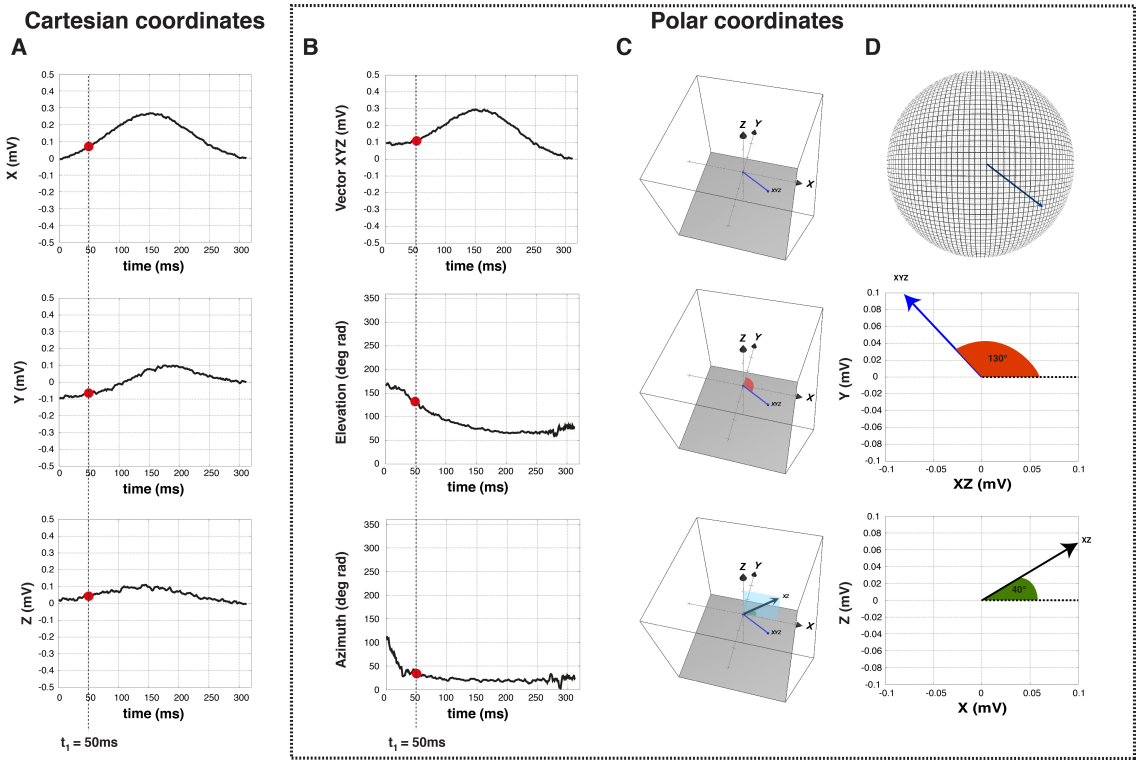

Abb. 6: Berechnung des gewichteten Azimuts und der gewichteten Elevation. Die kartesischen Koordinaten X, Y und Z **(A)** werden zuerst in eine Zeitfolge von polaren Koordinaten umgewandelt **(B)**. Für jeden Zeitpunkt (z.B. t_1 = 50ms) werden Azimut und Elevation mit der Länge multipliziert und der gewichtete Mittelwert wird als die Summe aller Produkte durch die Summe der Längen berechnet **(C und D)** [E].

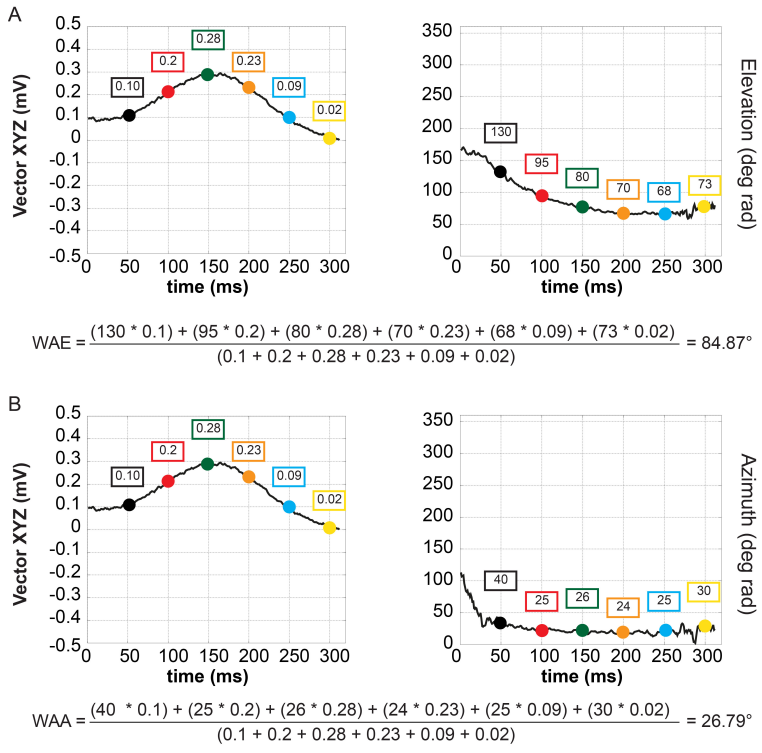

Abb. 7: Beispielrechnung eines gewichteten Azimuts **(A)**, sowie einer gewichteten Elevation **(B)** [E].

- In einem dritten Schritt wird jeweils der Winkel *dT°* zwischen zwei aufeinanderfolgenden T-Wellen-Vektoren berechnet (Gleichung 3 und Abb. 8) Dieser Winkel dient als Maß der momentanen Repolarisationsinstabilität.

$$dT° = acos[\sin(WAE_1) * \cos(WAA_1) * \sin(WAE_2) * \cos(WAA_2) + \cos(WAE_1) * \cos(WAE_2) + \sin(WAE_1) * \sin(WAA_1) * \sin(WAE_2) * \sin(WAA_2)] \quad (3)$$

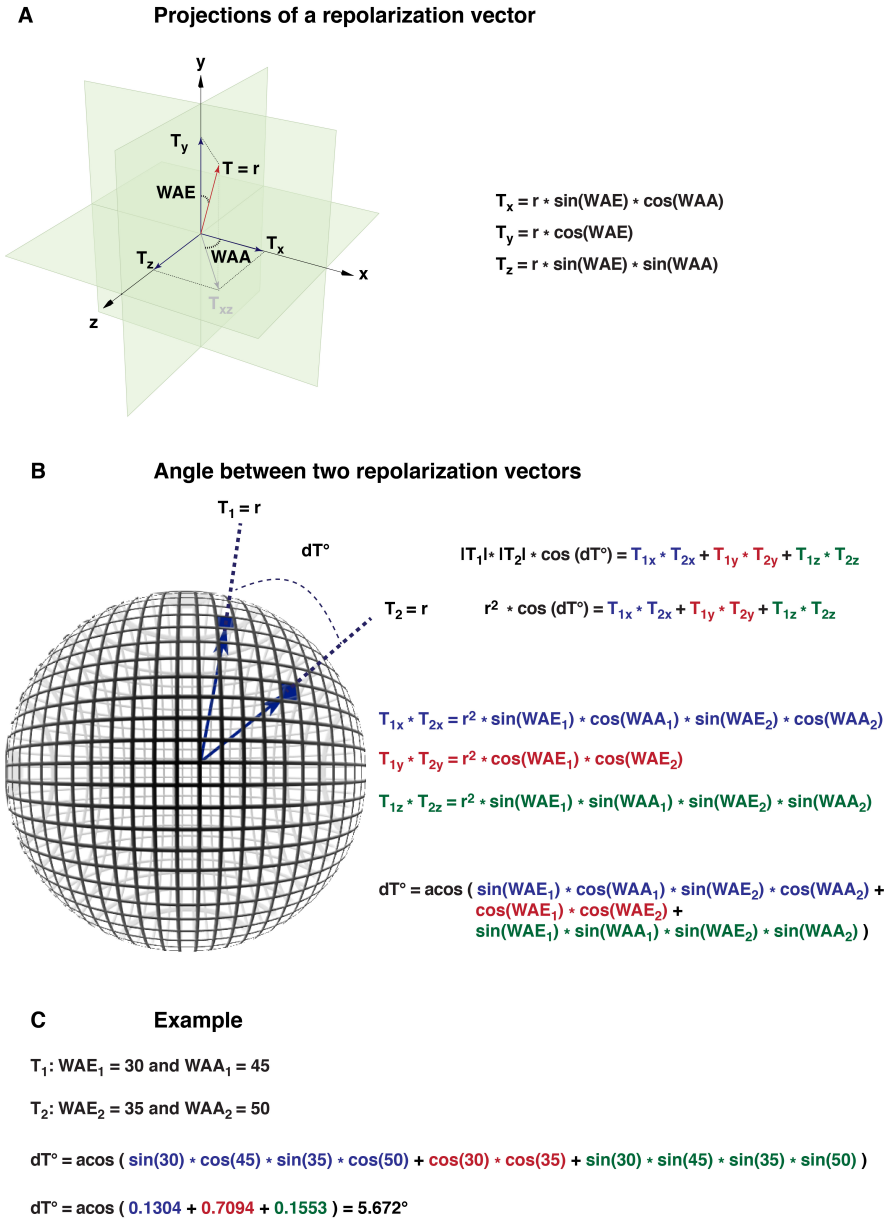

Abb. 8: (A) Projektion eines T-Wellen-Vektors auf zwei orthogonale Ebenen. **(B)** Berechnung des Winkels *dT°* zwischen zwei aufeinanderfolgenden T-Wellen-Vektoren (T_1 und T_2). **(C)** Beispielrechnung eines *dT°*-Winkels [E].

- Meist betragen die Winkeländerungen *dT*° von T-Welle zu T-Welle nur wenige Grad. Trägt man die Winkel jedoch über die Zeit auf, so demaskieren sich periodische *dT*°-Anstiege etwa alle 15–30 s. Die periodischen Komponente des *dT*°-Signals werden anschließend durch eine kontinuierliche Wavelet-Transformation quantifiziert. Die Koeffizienten der kontinuierlichen Wavelet-Transformation werden mit bereits etablierten Algorithmen in eine Pseudofrequenz überführt. Die PRD erfasst schließlich den Bereich zwischen 0 und 0,1 Hz der Pseudofrequenz und wird in deg^2 angegeben (Abb. 9) [E].

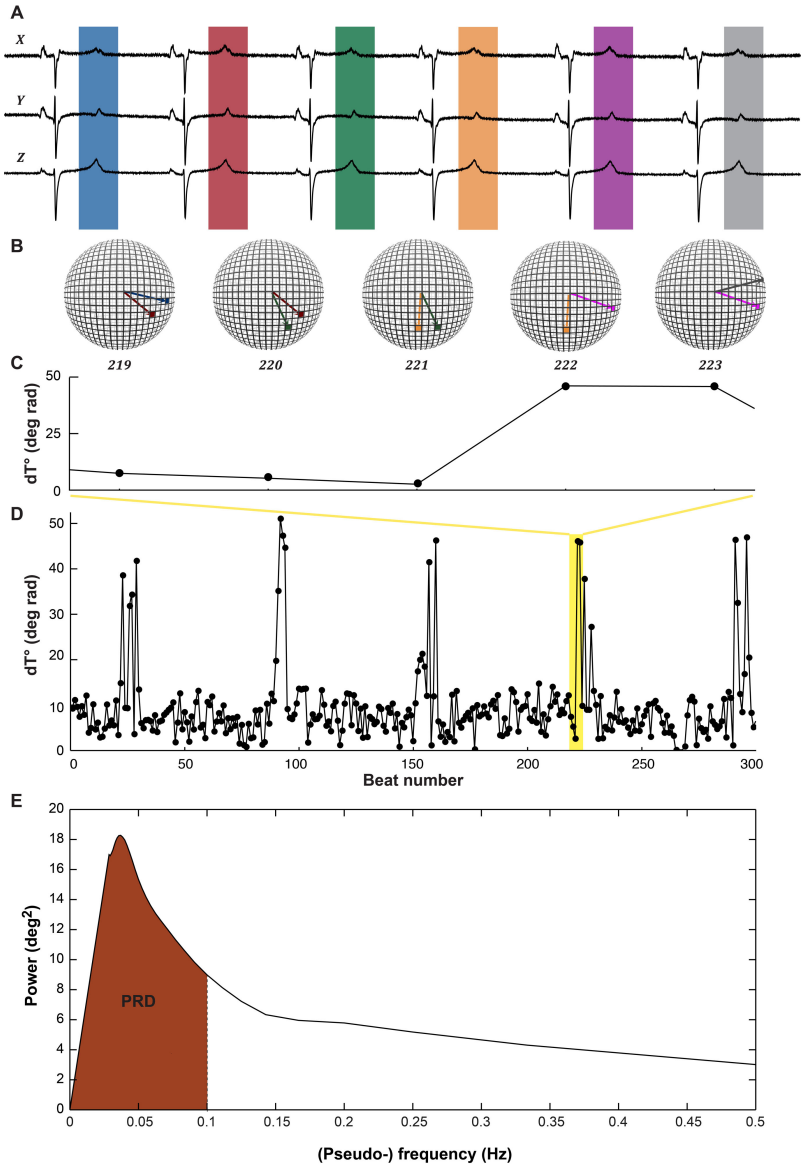

Abb. 9: (A) Schematische Darstellung der Berechnung der „Periodic Repolarization Dynamics“: **(A)** EKG in orthogonalen Frank-Ableitungen. **(B)** Winkel zwischen zwei T-Wellen-Vektoren. **(C und D)** periodische dT°-Anstiege. **(E)**, Wavelet- Transformation der periodischen *dT*°-Anstiege [E].

5.3.2. Pathophysiologischen Mechanismen der PRD

Die exakten pathophysiologischen Mechanismen, die PRD zugrunde liegen, sind noch nicht hinreichend erforscht. Experimentelle Befunde und theoretische Erkenntnisse sprechen jedoch dafür, dass PRD den Effekt niederfrequenter sympathischer Entladungen auf die kardiale Repolarisation des Ventrikelmyokards widerspiegelt [E,F,G]. Zuerst konnte in elektrophysiologischen Untersuchungen gezeigt werden, dass PRD unabhängig von der Herzfrequenzvariabilität ist (Abb. 10 und Abb. 12A) [E].

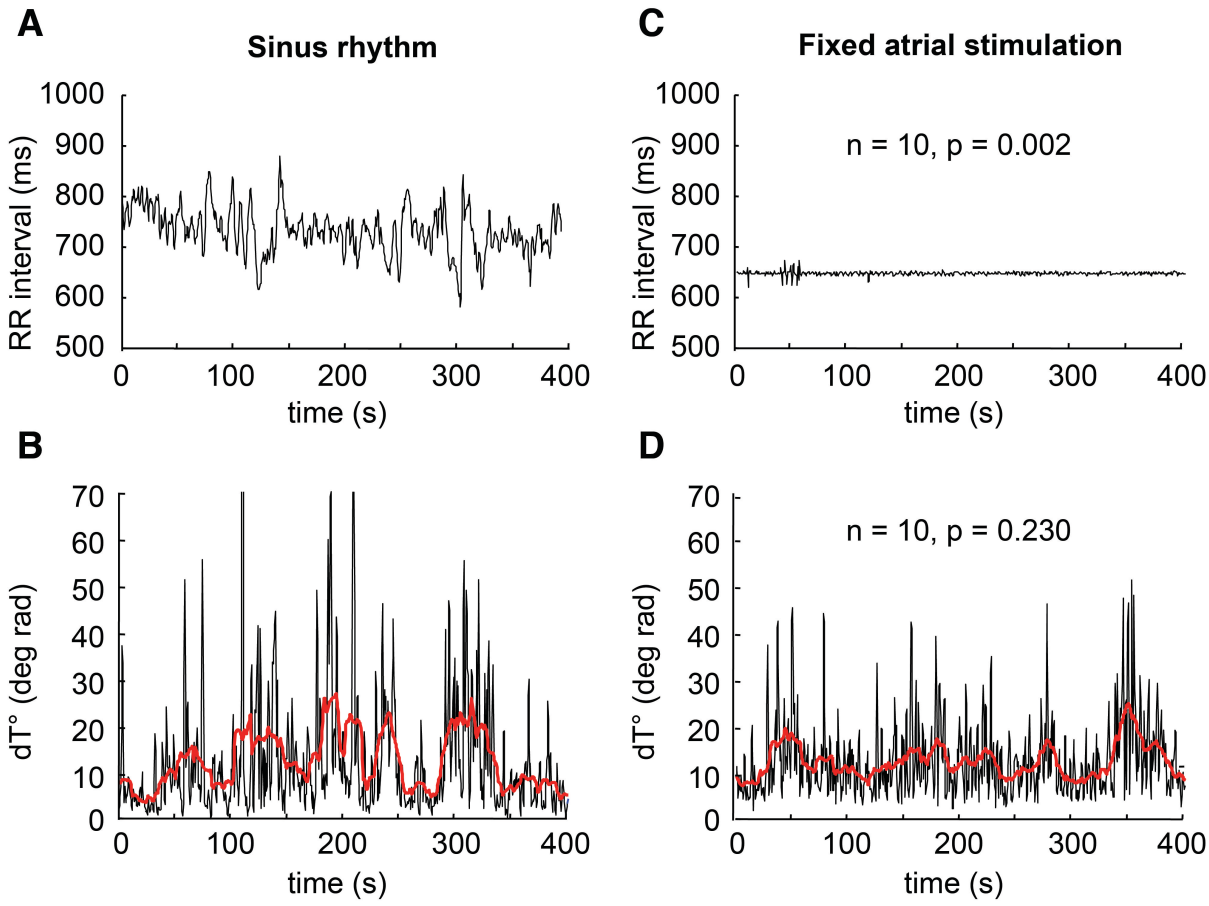

Abb. 10: Typisches RR-Intervall **(A)** und *dT*°-Signal **(B)** bei einem gesunden Probanden in Ruhe. **(C)** Fast vollständige Elimination der Herzfrequenzvariabilität unter atrialer Stimulation (bei n=10, p=0.002 für die Änderung der Herzfrequenzvariabilität unter Stimulation). **(D)** *dT*°-Signal mit erhaltener Variabilität im niederfrequenten Spektrum unter atrialer Stimulation (p=0.230 bei n=10) [E].

In einem zweiten Schritt konnte in einem Tiermodell gezeigt werden, dass PRD unabhängig von der Atmung war (Abb. 11) [E].

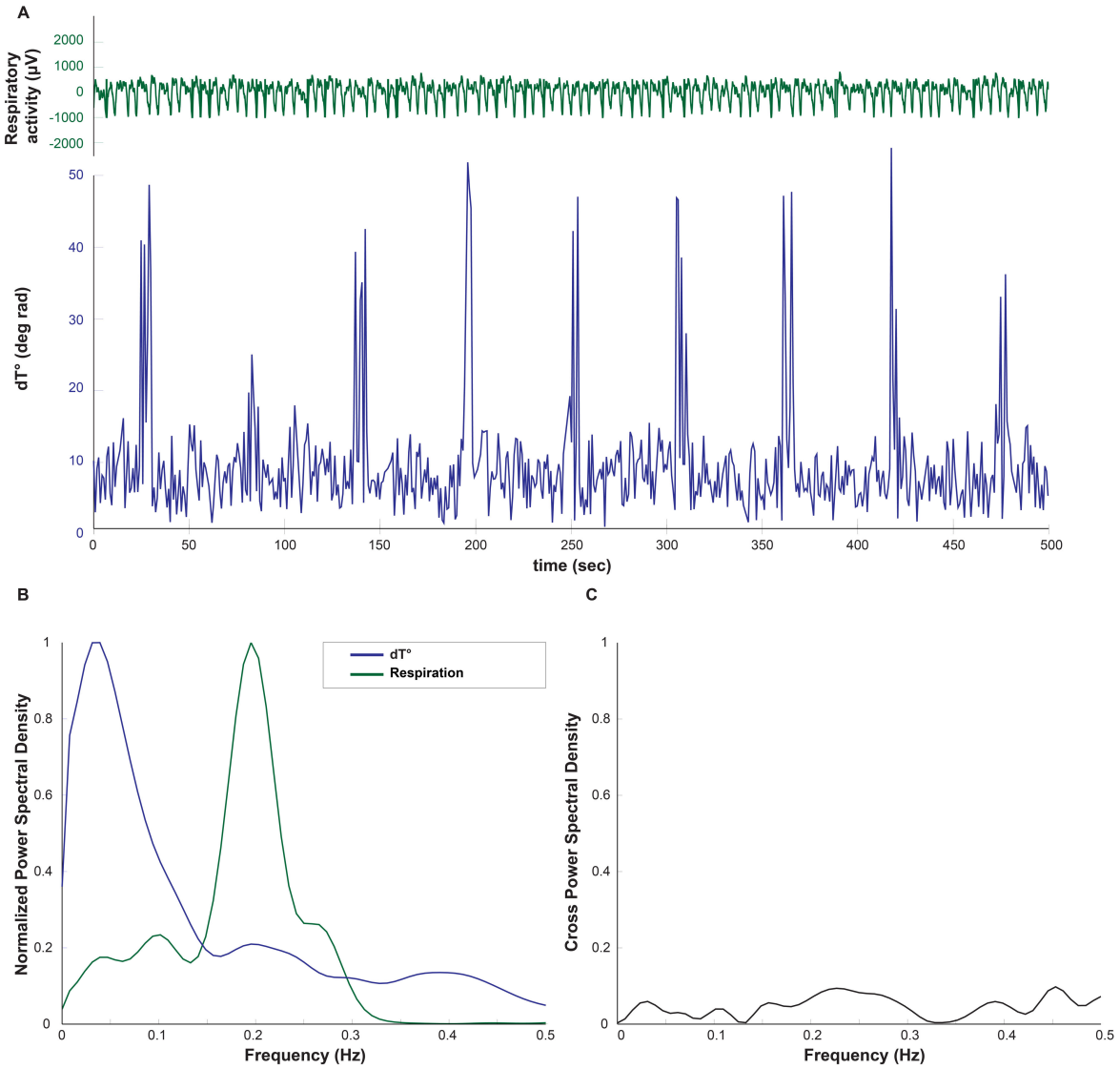

Abb. 11: Testung der Interaktion zwischen der Atmung und der PRD im Tiermodell. 7 Schweine wurden intubiert und mit fixierter Atemfrequenz, sowie fixiertem Tidalvolumen beatmet. **(A)** Das Atemsignal, das nicht invasiv durch einen Atemgürtel abgeleitet ist, wird mit grüner Farbe gekennzeichnet. Das *dT*°-Signal wird in Blau geplottet. **(B)** Spektralanalyse vom Atemsignal (grün) und *dT*°-Signal (blau). Es zeigen sich Peaks an unterschiedlichen Frequenzspektren (0.04 Hz für das *dT*°-Signal und 0.2 Hz für das Atemsignal), ohne signifikante Kreuzkorrelation in der Kreuzspektralanalyse **(C)** [E].

Der Effekt des sympathischen Nervensystems auf PRD ist mit physiologischen und pharmakologischen Provokationen untersucht worden. Eine physiologische sympathische Aktivierung durch körperliche Belastung oder mittels eines Kipptischversuchs führte bei Gesunden zu einer deutlichen Zunahme der PRD (Abb. 12 B und C). Verabreichung eines Betablockers unter atrialer Stimulation supprimierte dagegen die PRD (Abb. 12 D) [E].

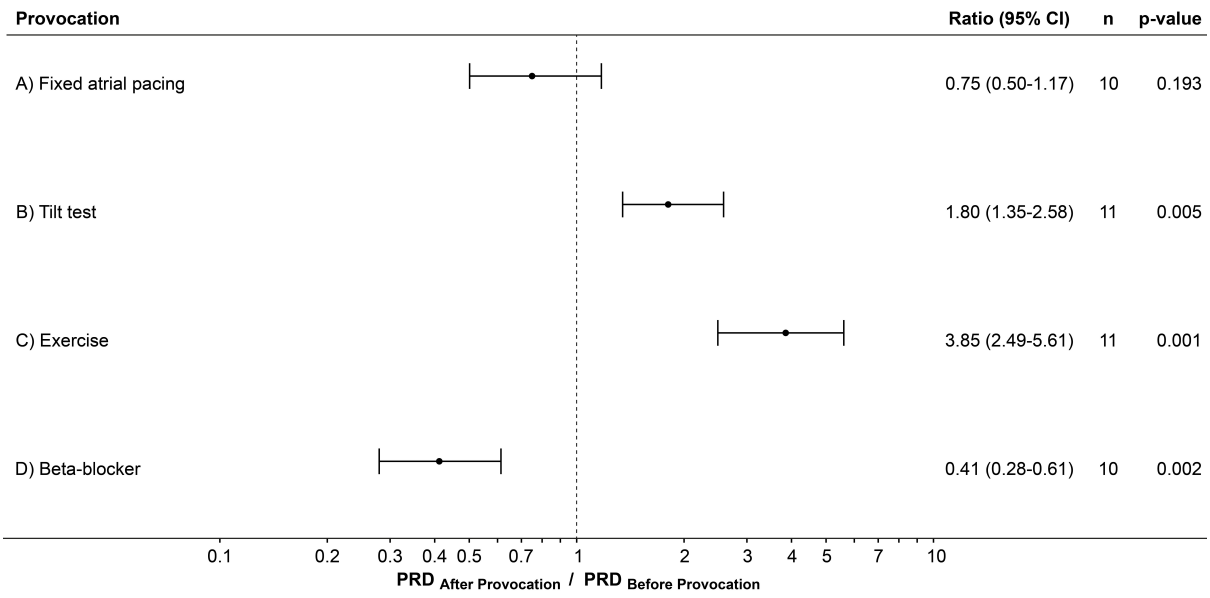

Abb. 12: Effekte der atrialen Stimulation **(A),** der Kipptischuntersuchung **(B),** der Belastung **(C)** und der Verabreichung eines Betablockers **(D)** auf PRD ^{E}.

Die niederfrequenten Oszillationen der kardialen Repolarisation[29] und ihr Zusammenhang mit der sympathischen Innervierung des Herzens[30] konnten auch von anderen Forschungsgruppen gezeigt werden. Hanson und Mitarbeiter konnten ein niederfrequentes oszillatorisches Verhalten der Aktionspotenzialdauer (APD) bei Patienten mit Herzinsuffizienz nachweisen[29]. Pueyo und Mitarbeiter konnten mit Hilfe einer Computermodellierung zeigen, dass eine phasische beta-adrenergische Stimulation zur Zunahme der niederfrequenten Oszillationen der Repolarisation führt[30].

Auf zellulärer Ebene verkürzt die sympathische Stimulation die APD der Kardiomyozyten. Unterschiedlich stark beeinflusst werden dabei die Zellen der einzelnen Schichten des Herzens[31]. So, verkürzt die sympathische Stimulation die APD der äußeren Myokardschichten stärker als die der mittleren Myokardschicht (transmurale Dispersion der Repolarisation)[32]. Die T- Welle des Oberflächen-EKGs ist die integrale Repräsentation der Phasen 2 und 3 der Aktionspotenziale aller Kardiomyozyten[33,34]. Die sympathische Aktivierung führt deswegen zu entsprechenden Mikrovoltänderungen der T-Welle, die mit bloßem Auge nicht sichtbar sind. Da efferente sympathische Aktivität am Herzen in niederfrequenten Clustern auftritt[28,35-38], sind sympathisch induzierte T-Wellen-Modulationen auch in diesem Frequenzbereich zu erwarten. Eine besondere Situation findet sich bei

Patienten nach Myokardinfarkt statt. Bei diesen Patienten können sich myokardiale Bereiche finden, deren Zellen zwar vital, jedoch autonom denerviert sind. Diese Zellen können nicht auf sympathische Stimulation reagieren, wodurch sich die transmurale Dispersion und dementsprechend die PRD erhöhen.

5.3.3. PRD bei Postinfarktpatienten mit erhaltener Pumpfunktion

Der prognostische Wert einer erhöhten PRD nach akutem Myokardinfarkt wurde in der ISAR-Risk-Studie an 908 Postinfarktpatienten getestet [E]. Einschlusskriterien waren das Vorhandensein eines Sinusrhythmus, ein Alter von 80 Jahren oder weniger und ein Herzinfarkt innerhalb der letzten 30 Tage. Bei allen Patienten wurde eine 30-minütige EKG-Aufzeichnung in Frank-Ableitungen und unter standardisierten Bedingungen durchgeführt. Der primäre Endpunkt der Studie war die 5-Jahres-Gesamtmortalität, als sekundärer Endpunkt ist die 5-Jahres kardiovaskuläre Mortalität definiert worden. Während des Beobachtungszeitraums starben 69 Patienten, 36 davon waren als kardiovaskulär bedinge Todesfälle klassifiziert. Abb. 13 zeigt repräsentative *dT*°-Signale eines Patienten der den Beobachtungszeitraum überlebt hat (A), sowie eines Patienten der einige Monate nach dem Herzinfarkt plötzlich verstorben ist (B). In den Signalen beider Patienten waren niederfrequente Oszillationen erkennbar, die jedoch bei dem verstorbenen Patienten deutlich ausgeprägter waren [E]. Dieser Unterschied bestand hochsignifikant in der gesamten Kohorte. So betrug die mediane PRD bei Überlebenden 2,66 deg^2 (IQR 3,93 deg^2), bei Verstorbenen hingegen 6,67 deg^2 (IQR 8,53 deg^2). Abb. 14 zeigt die kumulativen Mortalitätskurven bei Postinfarktpatienten stratifiziert nach der PRD. Die 227 Patienten mit PRD ≥5.75 deg^2 hatten eine 5-Jahresmortalität von 18.2% im Vergleich zu einer 4.1% 5-Jahres-Mortalität bei Patienten mit PRD <5.75 deg^2. Multivariable Cox-Regressionsanalysen zeigten, dass der prädiktive Wert der PRD unabhängig von anderen etablierten Risikoparametern wie der LVEF, dem GRACE-Score und klinischen Markern war (Tab. 2) [E].

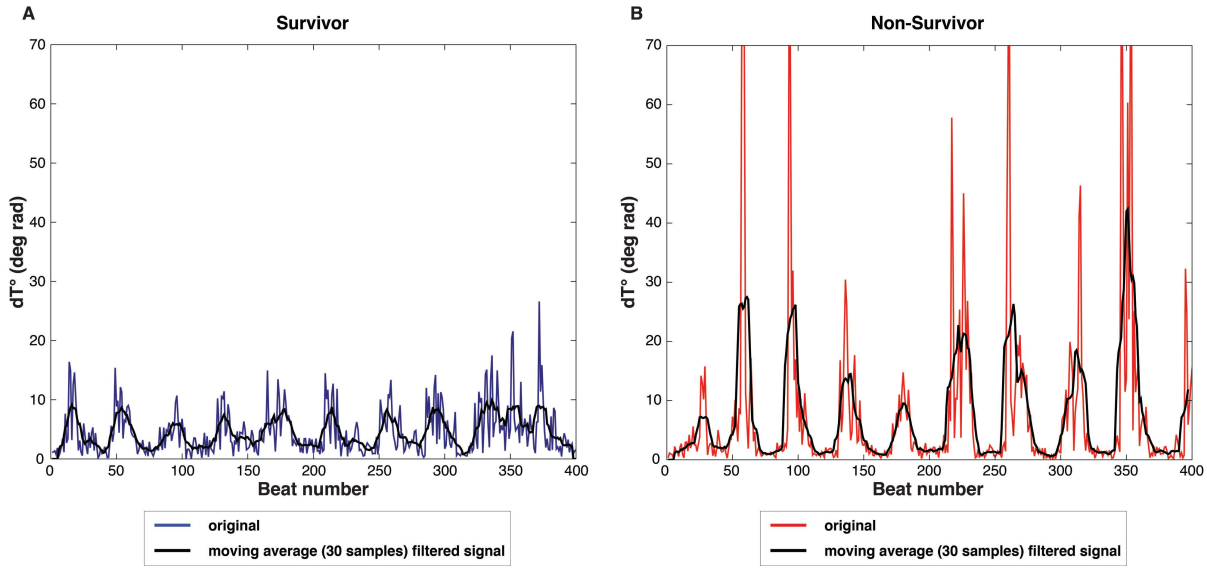

Abb. 13: Repräsentative *dT°*-Signale eines Patienten der den Beobachtungszeitraum überlebt hat **(A)**, sowie eines Patienten der einige Monate nach dem Herzinfarkt plötzlich verstorben ist **(B)**. In den Signalen beider Patienten waren niederfrequente Oszillationen erkennbar, die jedoch bei dem verstorbenem Patienten deutlich ausgeprägter waren [E].

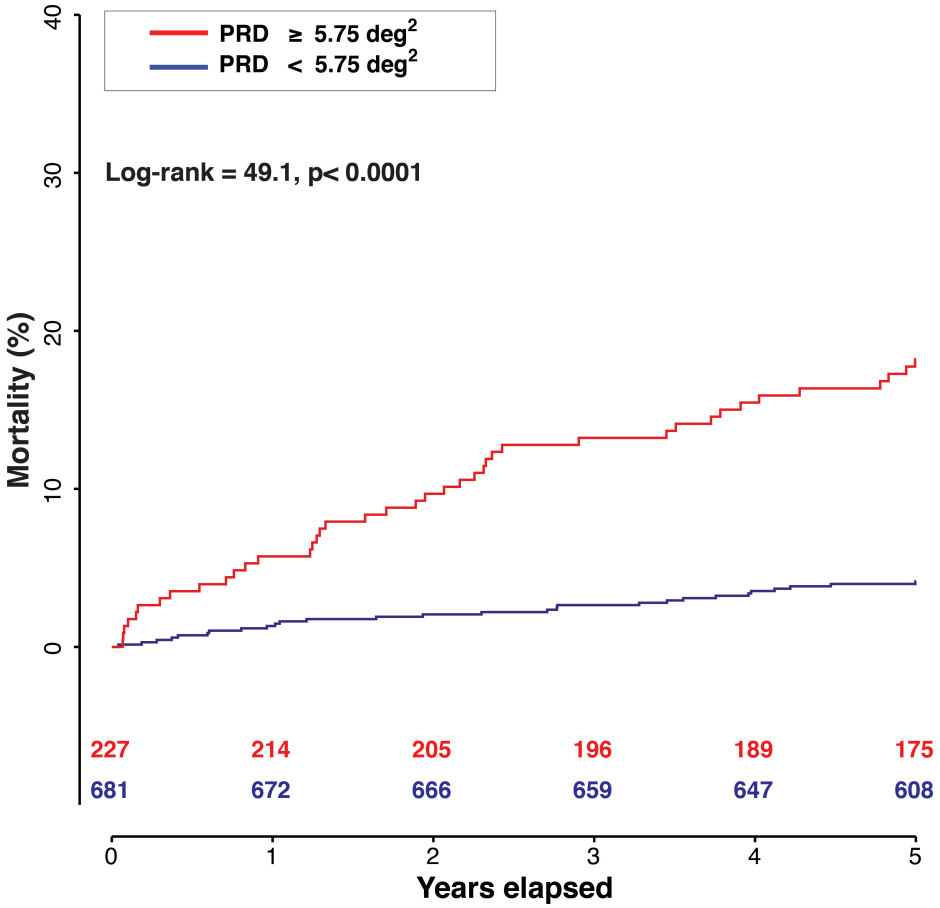

Abb. 14: Kumulative 5-Jahres-Mortalitätskurven stratifiziert nach PRD ≥5.75 deg² [E].

Tab. 2: Uni- und multivariable Cox-Regressionsanalyse für die Prädiktion der 5-Jahres Gesamtmortalität und der 5-Jahres-kardiovaskulären Mortalität bei 908 Postinfarkt-Patienten der ISAR-Risk Studie [E].

All-cause Mortality				
Risk variable	**Univariable Cox Regression**		**Multivariable Cox Regression**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
LVEF ≤ 35%	3.81 (2.23 – 6.51)	< 0.001	2.13 (1.22 – 3.70)	0.008
GRACE score ≥120	5.54 (3.24 – 9.46)	< 0.001	3.61 (2.06 – 6.31)	< 0.001
Diabetes mellitus	2.61 (1.61 – 4.23)	< 0.001	2.07 (1.25 – 3.41)	0.005
Mean HR > 75 bpm	1.98 (1.11 – 3.55)	0.020	1.10 (0.56 – 2.17)	0.783
SDNN ≤ 70 ms	2.01 (1.22– 3.33)	0.007	1.71 (0.96 – 3.07)	0.072
QTVI > -0.47	2.54 (1.55 – 4.19)	< 0.001	1.12 (0.65 – 1.93)	0.688
PRD ≥ 5.75 deg^2	4.75 (2.94 – 7.66)	< 0.001	3.03 (1.79 – 5.11)	< 0.001
Cardiovascular Mortality				
Risk variable	**Univariable Cox Regression**		**Multivariable Cox Regression**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
LVEF ≤ 35%	4.69 (2.32 – 9.50)	< 0.001	2.71 (1.30 – 5.67)	0.008
GRACE score ≥120	5.82 (2.75 –12.33)	< 0.001	3.80 (1.73 – 8.35)	< 0.001
Diabetes mellitus	2.72 (1.40 – 5.31)	0.003	2.16 (1.08 – 4.31)	0.029
Mean HR > 75 bpm	2.22 (1.02 – 4.86)	0.046	1.36 (0.55 – 3.38)	0.510
SDNN ≤ 70 ms	1.89 (0.93 – 3.82)	0.080	1.48 (0.65 – 3.36)	0.350
QTVI > -0.47	1.99 (1.02 – 3.88)	0.044	0.81 (0.39 – 1.70)	0.586
PRD ≥ 5.75 deg^2	4.50 (2.33 – 8.69)	< 0.001	2.99 (1.45 – 6.17)	0.003

GRACE = Global Registry Acute Coronary Events, LVEF = linksventrikuläre Auswurffraktion, QTVI = QT-Variabilitätsindex, PRD = Periodic Repolarization Dynamics

5.3.4. PRD bei Patienten mit Verdacht auf koronare Herzerkrankung

Der prädiktive Wert der PRD bei Patienten mit Verdacht auf koronare Herzerkrankung ist in der FINCAVAS (FINnisch CArdioVAScular) Studie an 2.965 Patienten evaluiert worden. Einschlusskriterien waren das Vorhandensein eines Sinusrhythmus**,** ein Alter zwischen 30 und 80 Jahren und die klinische Indikation zur Durchführung eines 12-Kanal-Belastungs-EKGs (GE CASE, 500 Hz). Patienten mit einer Vorbelastungsphase kürzer als 2.5 Minuten sind von der Studie ausgeschlossen worden. Der primäre Endpunkt der Studie war die Gesamtmortalität, der sekundäre Endpunkt war die kardiovaskuläre Mortalität. Zur Berechnung der PRD ist eine Konversion der Vorbelastungsphase mittels der inversen Dower's Transformation in die orthogonalen X, Y und Z Ableitungen ausgeführt worden. PRD ist mit T-Wellen-Alternans (TWA), das ein starker Mortalitätsprädiktor in dieser Studienpopulation war, verglichen worden[39]. TWA ist ein seit mehr als 100 Jahren bekanntes elektrokardiographisches Phänomen, das mikroskopische T-Wellen-Veränderungen im hochfrequenten Bereich (Schlag-zu-Schlag) erfasst[40]. Zur Berechnung des TWA in dieser Kohorte ist die MMA (modified moving average) Methode während der Belastungsphase ausgeführt worden[39,40].

Während eines mittleren Beobachtungszeitraums von 75 Monaten sind 309 Patienten verstorben. In der multivariablen Cox-Regressionsanalyse war PRD der stärkste Mortalitätsprädiktor und einer der stärksten Prädiktoren der kardiovaskulären Mortalität. Der prädiktive Wert der PRD, die in Ruhe erfasst werden konnte, war unabhängig vom TWA, das eine ergometrische Untersuchung erforderte (Tab. 3)[E]. Die negative Interaktion zwischen PRD und TWA deutet darauf hin, das PRD Hochrisikopatienten mit niedrigem TWA erfassen kann.

Tab. 3: Multivariable Cox-Regressionsanalyse für die Prädiktion der Gesamtmortalität und der kardiovaskulären Mortalität in 2.965 Patienten der FINCAVAS Studie [E].

Multivariable Cox Regression Analysis				
Risk variable	**All-cause mortality**		**Cardiovascular mortality**	
	Beta (95% CI)	**p-value**	**Beta (95% CI)**	**p-value**
Age, continuous	0.055 (0.042 – 0.068)	< 0.001	0.044 (0.027 – 0.063)	< 0.001
Sex (yes, no)	-0.535 (-0.280 – -0.790)	< 0.001	-0.960 (-0.531 – -1.386)	< 0.001
DM (yes, no)	-0.393 (-0.111 – -0.675)	0.006	-0.291 (-0.721 – 0.139)	0.184
Previous MI (yes, no)	0.205 (-0.049 – 0.459)	0.115	0.288 (-0.080 – 0.656)	0.126
Beta-blocker (yes, no)	0.350 (0.085 – 0.614)	0.010	0.582 (0.164 – 0.999)	0.006
TWA, continuous	0.175 (0.007 – 0.284)	0.002	0.274 (0.133 – 0.414)	< 0.001
PRD, continuous	0.198 (0.103 – 0.292)	< 0.001	0.269 (0.136 – 0.401)	< 0.001
TWA * PRD	-0.091 (-0.022 – -0.160)	0.010	-0.136 (-0.048 – -0.244)	0.002

DM = Diabetes mellitus, MI = Myokardinfarkt, TWA = T-Wellen-Alternans, PRD = Periodic Repolarization Dynamics

5.3.5. PRD bei Postinfarktpatienten mit eingeschränkter Pumpfunktion

Die prognostische Bedeutung der PRD bei Patienten mit einem Herzinfarkt älter als 30-Tage und einer hochgradig eingeschränkten LVEF ist in der Multicenter Automatic Defibillator Implantation Trial (MADIT-II) Studie untersucht worden [H]. In der MADIT-II Studie sind 1.232 Patienten mit einer LVEF ≤30% nach Myokardinfarkt ohne vorheriges Arrhythmieereignis 3:2 zu einer primärprophylaktischen ICD-Implantation oder einer medikamentösen Therapie randomisiert worden[8]. Der primäre Endpunkt der Studie war die Reduktion der 2-Jahres Mortalität. Die Studie musste frühzeitig abgebrochen werden, nachdem die ICD-Therapie zu einer signifikanten Senkung der Gesamtmortalität führte[8]. Die MADIT-II Studie führte zur Änderung der Leitlinien und Etablierung der primärprophylaktischen ICD-Implantation bei Postinfarktpatienten mit hochgradig eingeschränkter LVEF als Grad-1-Empfehlung[10]. In einer Post-hoc Analyse der MADIT-II Studie ist der prognostische Wert der PRD als Prädiktor der Gesamtmortalität, der kardiovaskulären Mortalität, des plötzlichen und des nicht-plötzlichen Herztodes bei Patienten mit hochgradig eingeschränkter LVEF untersucht worden [H]. Eingeschlossen sind Patienten mit Vorhandensein eines Sinusrhythmus, die vor der Randomisierung ein 10-minütiges Ruhe EKG in Masor-Likar-Ableitungen bekommen haben (Abb. 15). In uni- und multivariablen Cox-Regressionsanalysen war die erhöhte PRD einer der stärksten Prädiktoren der Gesamtmortalität (Abb. 16 und Tab. 4), der kardiovaskulären Mortalität (Tab. 4), des plötzlichen (Tab. 5), sowie auch des nicht-plötzlichen Herztodes (Tab. 5). Des Weiteren ist der Effekt der ICD-Therapie bei Postinfarktpatienten stratifiziert nach PRD-Quartilen evaluiert worden. Die ICD-Therapie führte zu einer signifikanten Reduktion des plötzlichen Herztodes in allen PRD-Quartilen (Abb. 17C und 17D). Allerdings führte die ICD-Therapie zu einer Reduktion der Gesamtmortalität nur in den untersten drei PRD-Quartilen (Abb. 17A und 17B). Patienten mir sehr hohen PRD-Werten konnten von der primärprophylaktischen ICD-Implantation hinsichtlich der Gesamtmortalität nicht profitieren (17D), da die Reduktion des plötzlichen durch einen proportionalen Anstieg des nicht-plötzlichen Herztodes ausgeglichen worden ist [H].

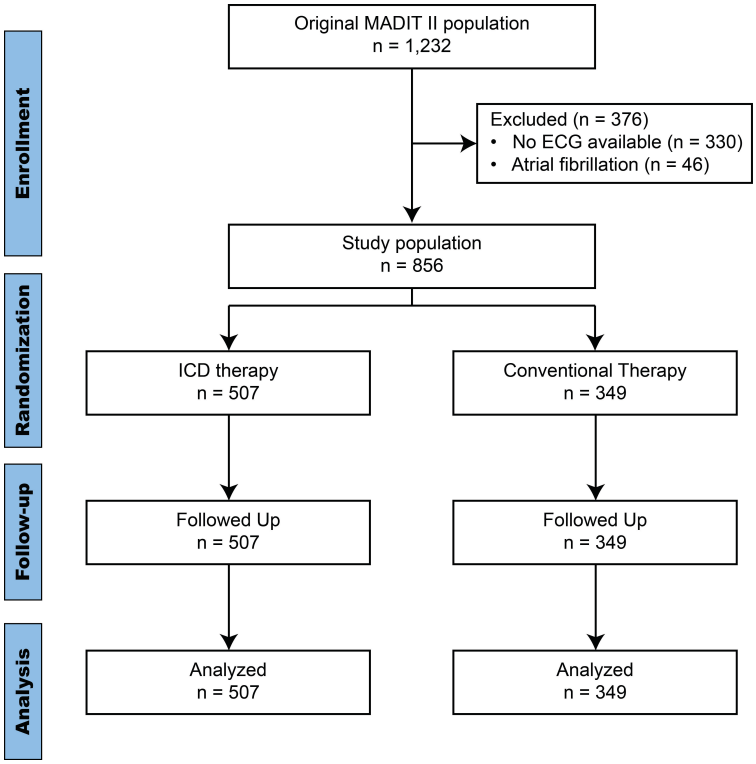

Abb. 15: Flussdiagramm der MADIT-II Studienpopulation [H].

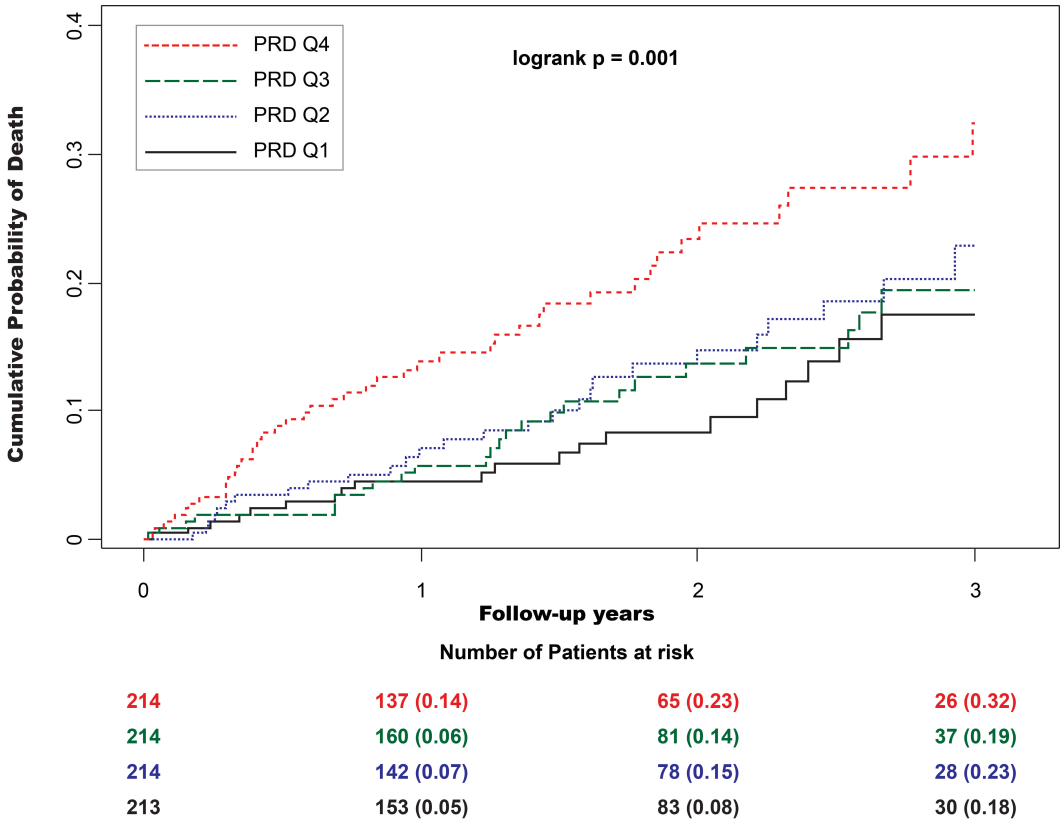

Abb. 16: Kumulative Mortalitätskurven bei Patienten in der MADIT-II Studie stratifiziert nach PRD-Quartilen [H].

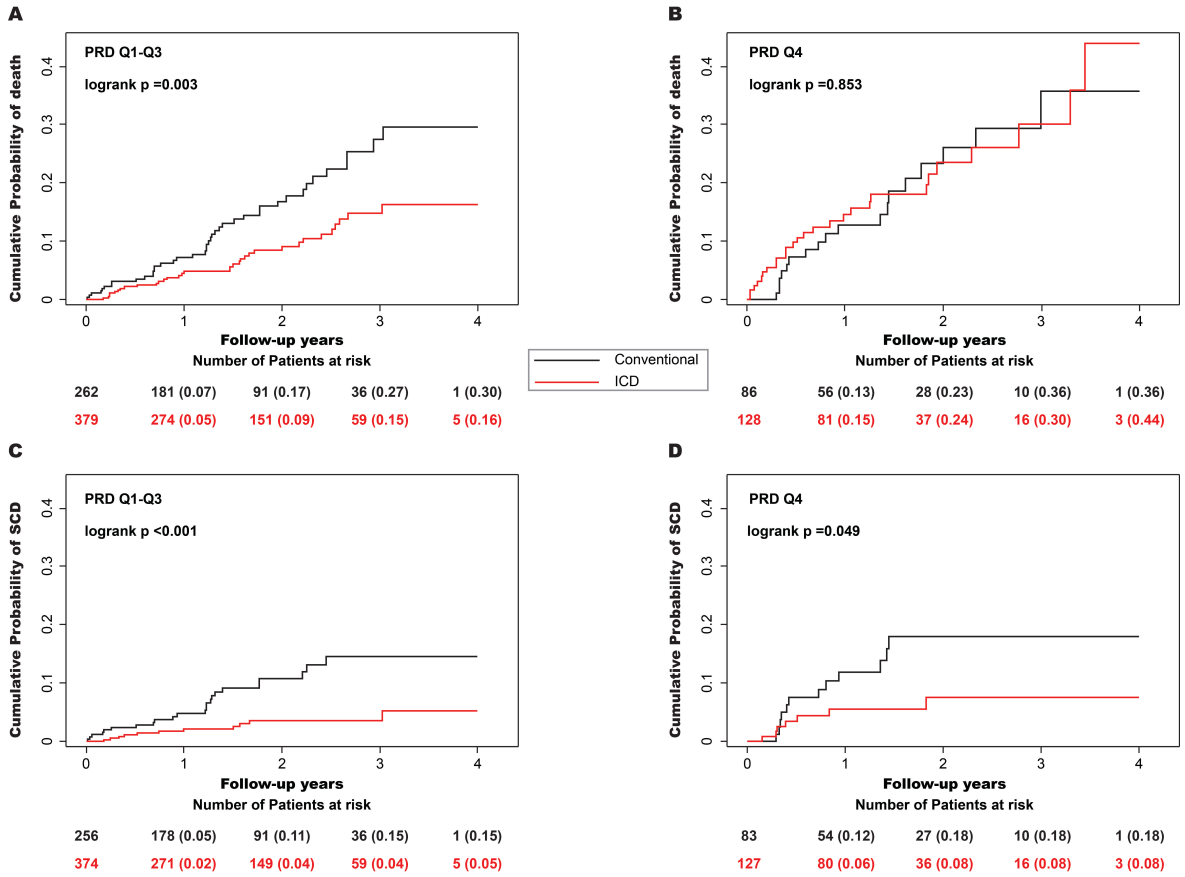

Abb. 17: Effekt der ICD-Therapie hinsichtlich der Gesamtmortalität **(A und B)** und des plötzlichen Herztodes bei Patienten mit unterschiedlichen PRD-Werten (**A und C:** PRD-Quartile 1-3**, B und D:** PRD-Quartil 4) [H].

Tab. 4: Multivariable Analyse für die Prädiktion der Gesamt- und kardiovaskulären Mortalität in der MADIT-II Studie [H].

Risk predictors	**Death**			**Cardiac Death**		
	HR (95% CI)	**X^2**	**p-value**	**HR (95% CI)**	**X^2**	**p-value**
Tx with ICD	0.66 (0.46 – 0.95)	5.0	0.026	0.57 (0.38 – 0.85)	7.7	0.006
PRD (deg^2), per SD	1.37 (1.19 – 1.59)	17.7	<0.001	1.39 (1.19 – 1.63)	16.8	<0.001
LVEF (%), per SD	0.91 (0.76 – 1.09)	1.0	0.313	0.89 (0.73 – 1.08)	1.4	0.245
NYHA class ≥II	1.08 (0.73 – 1.60)	0.2	0.694	1.16 (0.76 – 1.78)	0.5	0.500
Diabetes mellitus	1.17 (0.80 – 1.72)	0.7	0.407	1.25 (0.83 – 1.89)	1.2	0.281
BUN >25 mg/dl	2.26 (1.54 – 3.31)	17.2	<0.001	2.24 (1.48 – 3.39)	14.4	<0.001
Beta-blockers	0.63 (0.44 – 0.92)	5.8	0.016	0.62 (0.42 – 0.93)	5.3	0.022
QRS (s), per SD	1.42 (1.19 – 1.69)	15.2	<0.001	1.42 (1.17 – 1.71)	12.8	<0.001

LVEF = linksventrikuläre Auswurffraktion, PRD = Periodic Repolarization Dynamics, Tx = Therapie

Tab. 5: Multivariable Analyse für die Prädiktion des plötzlichen und des nicht plötzlichen Herztodes in der MADIT-II Studie [H].

Risk predictors	SCD			N-SCD		
	HR (95% CI)	X^2	p-value	HR (95% CI)	X^2	p-value
Tx with ICD	0.33 (0.19 – 0.58)	14.5	<0.001	1.41 (0.68 – 2.91)	0.9	0.351
PRD (deg^2), per SD	1.40 (1.13 – 1.75)	9.1	0.003	1.41 (1.10 – 1.81)	7.4	0.006
LVEF (%), per SD	0.79 (0.61 – 1.03)	3.0	0.082	1.22 (0.86 – 1.74)	1.2	0.266
NYHA class ≥II	1.31 (0.72 – 2.41)	0.8	0.379	1.47 (0.68 – 3.17)	0.9	0.330
Diabetes mellitus	1.25 (0.71 – 2.21)	0.6	0.407	1.16 (0.58 – 2.31)	0.2	0.684
BUN >25 mg/dl	1.71 (0.96 – 3.06)	3.3	0.070	3.65 (1.79 – 7.41)	12.8	<0.001
Beta-blockers	0.68 (0.39 – 1.18)	1.9	0.166	0.63 (0.32 – 1.25)	1.7	0.189
QRS (s), per SD	1.25 (0.95 – 1.64)	2.6	0.106	1.61 (1.16 – 2.22)	8.3	0.004

LVEF = linksventrikuläre Auswurffraktion, N-SCD = nicht-plötzlicher Herztod, PRD = Periodic Repolarization Dynamics, SCD = plötzlicher Herztod, Tx = Therapie

5.4. Kardiales Autonomes Versagen

Die Kombination einer erhöhten PRD, als Marker der sympathischen Überfunktion und einer supprimierten DC als Marker des vagalen Verlustes identifiziert eine neue Hochrisikogruppe mit einer schweren autonomen Dysfunktion, die als kardiales autonomes Versagen (cardiac autonomic failure; CAF) definiert wird [I]. Bei Patienten mit erhaltener LVEF >35% war die Kombination der abnormalen PRD und DC (CAF = 2) im Vergleich zur normalen PRD und DC (CAF 0) mit einem 10-fachen 5-Jahres Mortalitätsrisiko assoziiert (Abb. 18 und Tab. 6 Tab. 6) [I].

Tab. 6: Univariable Cox-Regressionsanalyse für die Prädiktion der 5-Jahres Mortalität bei Patienten nach akutem Myokardinfarkt mit erhaltener linksventrikulärer Pumpfunktion [I].

Risk variables	**Hazard ratio (95% CI)**	**p-value**
CAF 1 vs. CAF 0	3.4 (1.7 – 6.7)	< 0.001
CAF 2 vs. CAF 0	9.9 (5.0 – 19.6)	< 0.001
DC ≤ 2.5ms	4.9 (2.9 – 8.6)	< 0.001
PRD ≥ 5.75 deg^2	4.1 (2.4 – 7.1)	< 0.001
LVEF ≤ 45%	1.6 (0.8– 3.0)	0.171

CAF = kardiales autonomes Versagen, DC = Dezelerationskapazität, PRD = periodic repolarization dynamics. CAF 0 = PRD <5.75 deg^2 und DC >2.5ms, CAF 1 = PRD ≥5.75 deg^2 oder DC ≤2.5ms, CAF 2 = PRD ≥5.75 deg^2 und DC >2.5ms

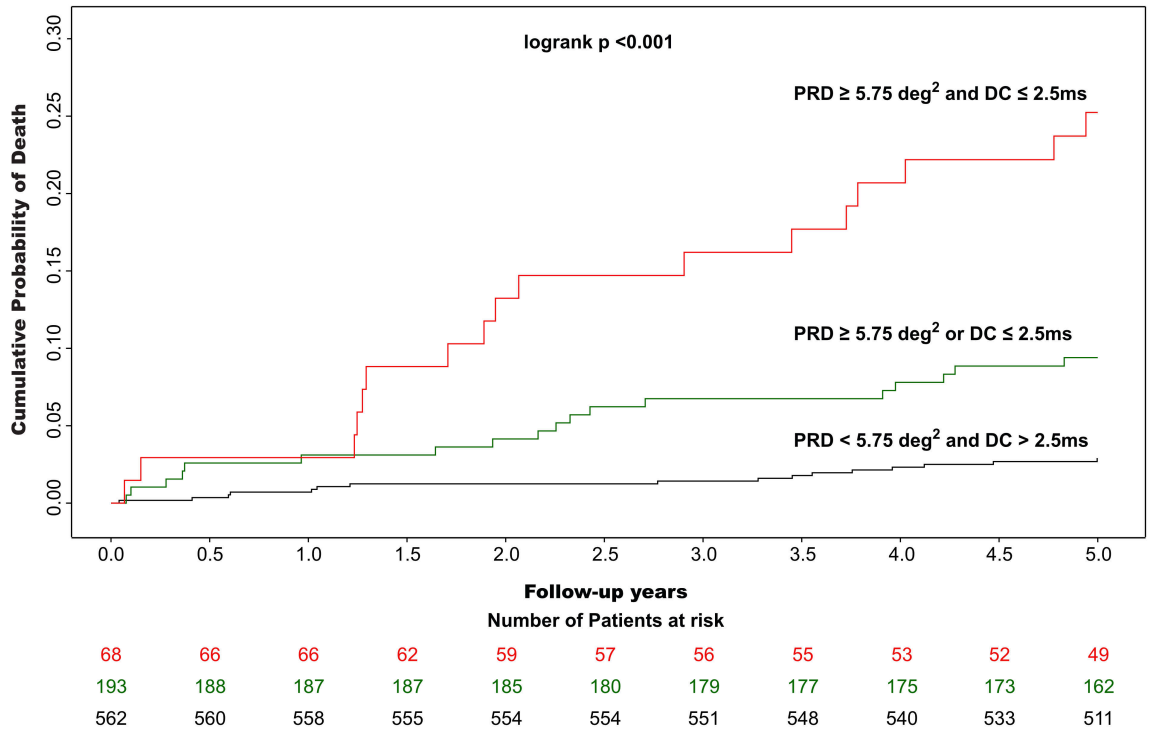

Abb. 18: Kumulative Mortalitätskurve bei Patienten nach Akutem Myokardinfarkt mit erhaltener Pumpfunktion stratifiziert nach kardialem autonomen Versagen [I].

6. Neue Ansätze zur Risikostratifizierung bei struktureller Herzerkrankung

Der prognostische Wert der Kombination der abnormalen Dezelerationskapazität und der abnormalen Herzfrequenzturbulenz des Herzens, die als schwere autonome Dysfunktion (severe autonomic failure, SAF) bezeichnet wird, ist bei Patienten mit höhergradiger Aortenklappenstenose (AS) getestet worden [J]. Insgesamt sind 216 Patienten mit symptomatischer hochgradiger Aortenklappenstenose, die einem transfemoralen oder operativen Aortenklappenersatz unterzogen, untersucht worden. Der primäre Endpunkt der Studie war die 2-Jahres-Gesamtmortalität. Als sekundärer Endpunkt ist die Kombination aus kardiovaskulärer Mortalität und Herzinsuffizienz-assoziierte Hospitalisierung definiert worden. 29 und 37 haben den primären, beziehungsweise den sekundären Endpunkt erreicht. Die 32 Patienten mit schwerer autonomer Dysfunktion und hochgradiger symptomatischer AS zeigten eine 50.0% Gesamtmortalität verglichen mit einer 10.7% Gesamtmortalität bei den 184 SAF-negativen Patienten (Abb. 19A). SAF war auch mit dem sekundären Endpunkt signifikant assoziiert (Abb. 19B). Multivariable Analysen zeigten, dass SAF der stärkste Mortalitätsprädiktor in dieser Kohorte war. Der prädiktive Wert der SAF war unabhängig von etablierten Mortalitätsprädiktoren bei AS, wie der logistische Euroscore, ein erhöhtes natriuretisches Peptid typ B, die Klappenöffnungsfläche und der mittlere Druckgradient über der Aortenklappe (Tab. 7) [J].

Ein klinisches Merkmal der Spätphase der Aortenklappenstenose ist die ausgeprägte Aktivierung des sympathischen Nervensystems[41]. Dies könnte in einer Kohorte mit 139 Patienten mit höhergradiger AS gezeigt werden. Im Vergleich zu Alter und Geschlecht gematchte Postinfarktpatienten wiesen Patienten mit mittel- und hochgradiger AS deutlich erhöhte PRD Werte auf (6.04 ± 3.80 deg^2 gegen 5.06 ± 4.24 deg^2 bei Postinfarktpatienten; $p = 0.019$) [K]. Abb. 20 zeigt ein repräsentatives *dT*°-Signal bei einem Patienten mit hochgradiger AS. Eine erhöhte PRD konnte in dieser Arbeit zur Identifizierung von Hochrisikopatienten mit AS führen, die bei konventionellen klinischen, echokardiographischen und elektrokardiographischen Kriterien nicht erkennbar waren.

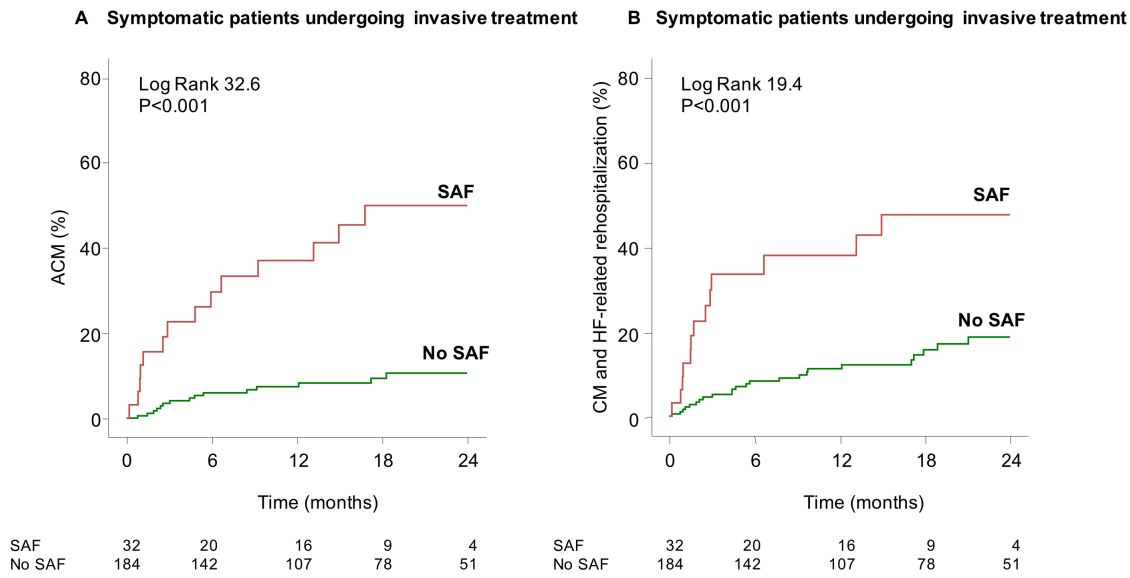

Abb. 19: Kaplan-Meier Analyse für die Prädiktion der Gesamtmortalität, sowie des kombinierten Endpunktes bestehend aus kardialer Mortalität und Herzinsuffizienz-assoziierter Hospitalisierung bei 216 symptomatischen Patienten mit hochgradiger Aortenklappenstenose, die einem operativen oder interventionellen Aortenklappenersatz unterzogen [J].

Tab. 7 Univariable und multivariable Cox Regressionsanalyse für die Prädiktion der Gesamtmortalität bei 216 symptomatischen Patienten mit hochgradiger Aortenklappenstenose, die einem operativen oder interventionellen Aortenklappenersatz unterzogen [J].

Risk variable	**Univariable Cox Regression**		**Multivariable Cox Regression**	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Logistic EuroSCORE ≥11%	4.5 (1.4 – 14.8)	0.014	2.8 (0.8 – 9.8)	0.098
BNP positive	2.1 (1.0 – 4.5)	0.041	2.7 (1.2 – 5.9)	0.013
Mean Gradient ≥ 43mmHg	0.6 (0.3 – 1.2)	0.142	0.5 (0.2 – 1.2)	0.125
AVA ≤ 0.7 cm^2	1.2 (0.6 – 2.7)	0.590	1.5 (0.7 – 3.5)	0.322
SAF	6.4 (3.1– 13.2)	< 0.001	5.6 (2.6 – 12.0)	< 0.001

AVA = Aortenklappenöffnungsfläche, BNP = Natriuretisches Peptid typ B, SAF = schwere autonome Dysfunktion

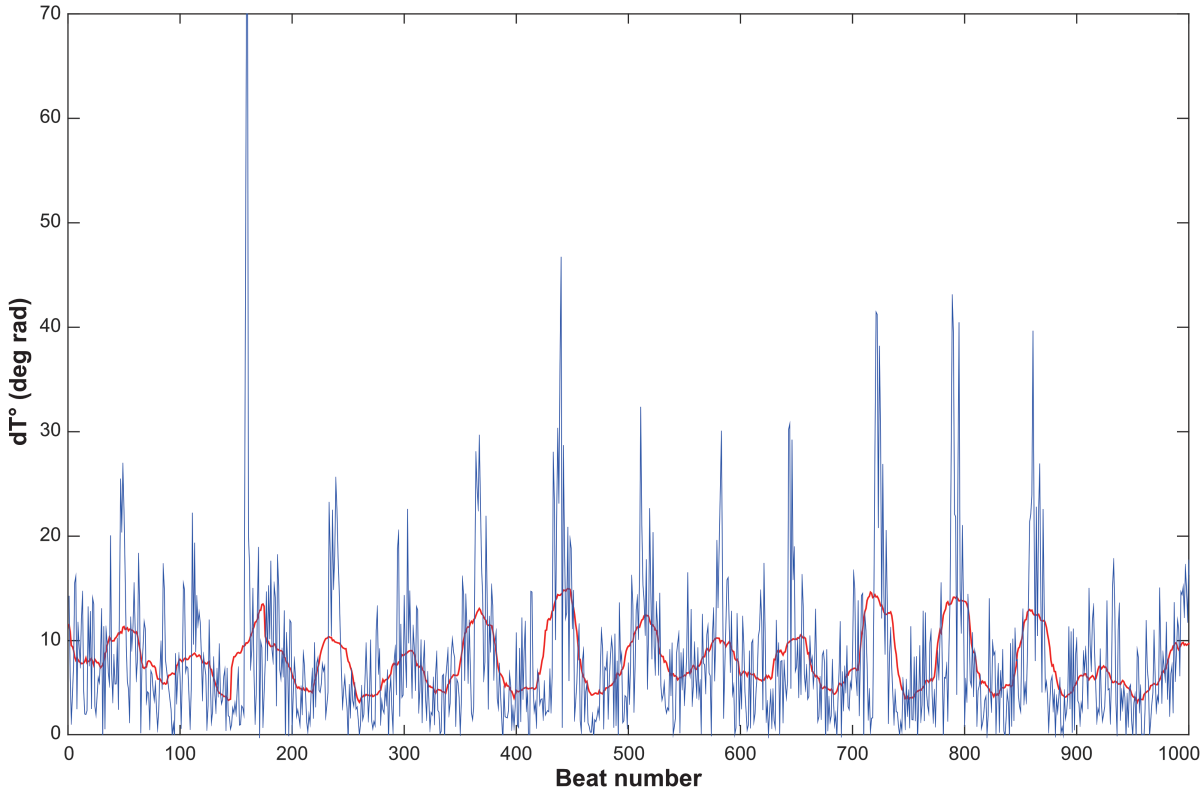

Abb. 20: Repräsentatives *dT*°-Signal bei einem Patienten mit hochgradiger Aortenklappenstenose [K].

7. Neue Therapieansätze bei Patienten mit ischämischer Kardiomyopathie

7.1. SMART-MI Studie

SMART-MI (Implantable cardiac monitorS in high-risk post-infarction patients with cardiac autonoMic dysfunction And modeRaTely reduced left ventricular ejection fraction; clinicaltrials.gov NCT02594488) ist eine prospektive, randomisierte, kontrollierte Studie, die Postinfarktpatienten mit LVEF 35–50% auf eine kardiale autonome Dysfunktion testet. Patienten mit erhöhter PRD oder eingeschränkter DC sind als Risikopatienten betrachtet und werden 1:1 auf die Implantation eines Ereignisrekorders mit telemetrischer Überwachung oder eine konventionelle Therapie randomisiert (Abb. 21) [L]. Der primäre Endpunkt der Studie ist die Erkennung von vordefinierten Arrhythmien, beziehungsweise das Auftreten von Vorhofflimmern mit einer Dauer ≥6 Minuten, die Detektion einer höhergradigen AV-Blockierung (AV-Block II° typ Mobitz, oder AV-Block III°) oder das Auftreten einer anhaltenden oder nicht-anhaltenden (≥12 Sek) Kammertachykardie. Zu den sekundären Endpunkten gehören die Gesamtmortalität, die kardiovaskuläre Mortalität, thromboembolische Ereignisse, ein Sinusarrest mit Dauer ≥6 Sekunden, nicht-anhaltende ventrikuläre Kammertachykardien mit einer Dauer von mindestens 12 Komplexen, sowie der kombinierte Endpunkt aus Gesamtmortalität, thromboembolischen Ereignissen und Hospitalisierung infolge einer akuten kardialen Dekompensation. Entdeckt man eine der vordefinierten Arrhythmien, so erfolgt innerhalb von 48h eine spezifische Intervention – entsprechend definierter Behandlungspfade im Sinne eines multifaktoriellen Ansatzes. Die mediane Nachbeobachtungszeit der Studie wird 18 Monate sein [L].

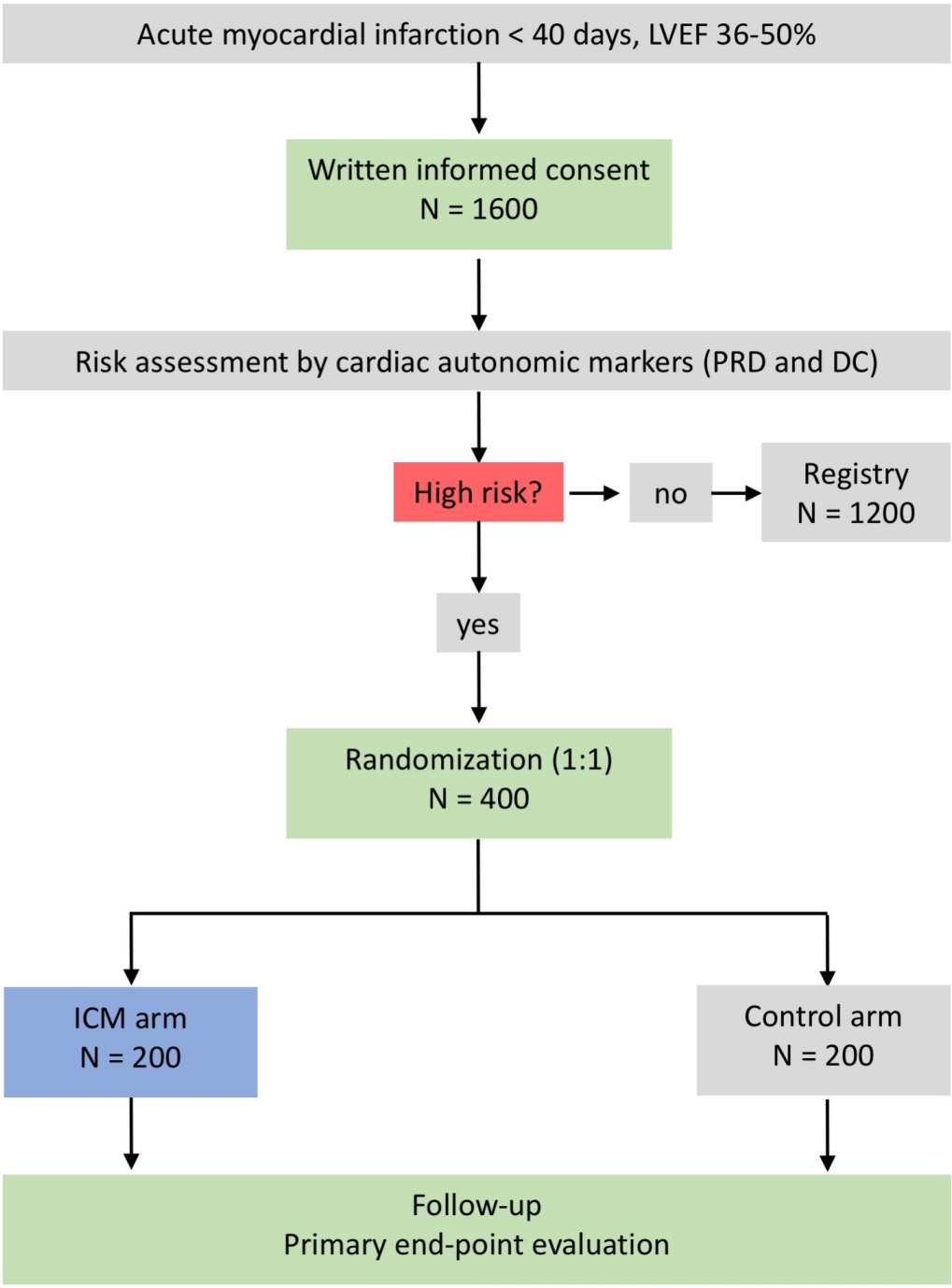

Abb. 21: Flussdiagramm der SMART-MI Studie [L].

7.2. Neue Therapieansätze in der Revaskularisationstherapie

Die Wiederherstellung und die Bewahrung einer ausreichenden myokardialen Durchblutung sind die zentralen Zielsetzungen in der Therapie der koronaren Herzerkrankung. Die Stentimplantation hat sich gegenüber der alleinigen perkutanen transluminalen Koronarangioplastie (PTCA) aufgrund des besseren angiographischen Primärergebnisses und der geringeren Zahl von In-Stent-Restenosen etabliert. Die Stents, die anfangs aus unbeschichtetem Metall (bare-metal stents) bestanden, sind gegenwärtig mit einem Polymer beschichtet, der ein Zytostatikum oder Immunsuppressivum enthält und dieses allmählich freigibt (drug-eluting Stents, DES). Dies hemmt die Bildung der Neointima, wodurch es zu weniger Restenosen kommt. Die Interaktion der Polymerbeschichtung mit der Gefäßwand kann jedoch zu einer Entzündungsreaktion und Neoatherosklerose führen[42]. Der Einsatz von biodegradierbaren Polymeren (BP) hat vielversprechende Resultate gezeigt, weil die Entzündungsreaktion geringer als bei den persistierenden Polymeren ausfällt[42]. In einer großen Metaanalyse, die 16 randomisierte kontrollierte Studien mit insgesamt 25.000 Patienten einbezog, konnte gezeigt werden, dass BP-Stents den PP-Stents hinsichtlich der Einjarhres-Sicherheits- (Tod, Stentthrombose und Myokardinfarkt) und Wirksamkeits-Endpunkten (Revaskularisation der Target Läsion) nicht unterlegen waren (Abb. 22, 23, 24 und 25) **M**. Darüber hinaus waren die BP-Stents den PP-Stents in Bezug auf die sehr späte Spätthrombose-Rate überlegen (Abb. 26) **M**.

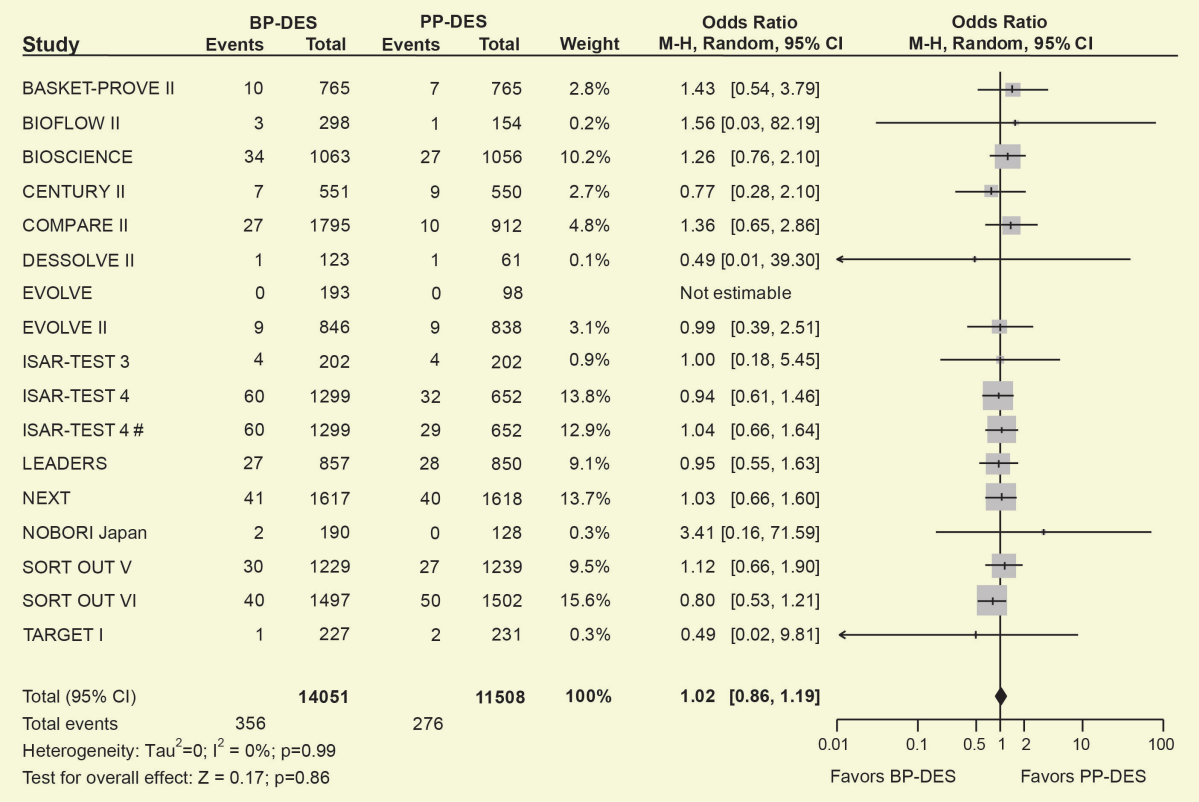

Abb. 22: Metaanalyse der Assoziation zwischen der Einjahres-Gesamtmortalität und der Therapie mit drug-eluting Stents (DES) mit biodegradierbaren Polymeren (BP-DES) gegen DES mit persistierenden Polymeren (PP-DES) [M]. BASKET-PROVE II trial = Safety and Efficacy Study Comparing 3 New Types of Coronary Stents[43], BIOFLOW II trial = Study of the Orsiro Drug Eluting Stent System[44], BIOSCIENCE trial = Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents[45], CENTURY II trial = Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease[46], COMPARE II trial = Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent[47], DESSOLVE II trial = Clinical Investigation of the MiStent DES in Coronary Artery Disease[48], EVOLVE and EVOLVE II trials = Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s)[49,50], ISAR-TEST 3 trial = Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis[51], ISAR-TEST 4 trial = 3 Limus Agent Eluting Stents With Different Polymer Coating[52], LEADERS trial, Limus Eluted From a Durable Versus Erodable Stent Coating[53], NEXT trial, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial[54], NOBORI Japan trial = Nobori Biolimus A9-Eluting Stent versus Sirolimus-Eluting Stent in Patients With Stenosis in Native Coronary Arteries[55], SORT-OUT V trial = Randomised Clinical Comparative Study of the Nobori and the Cypher Stent[56], SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity Stents[57]. TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V[58].

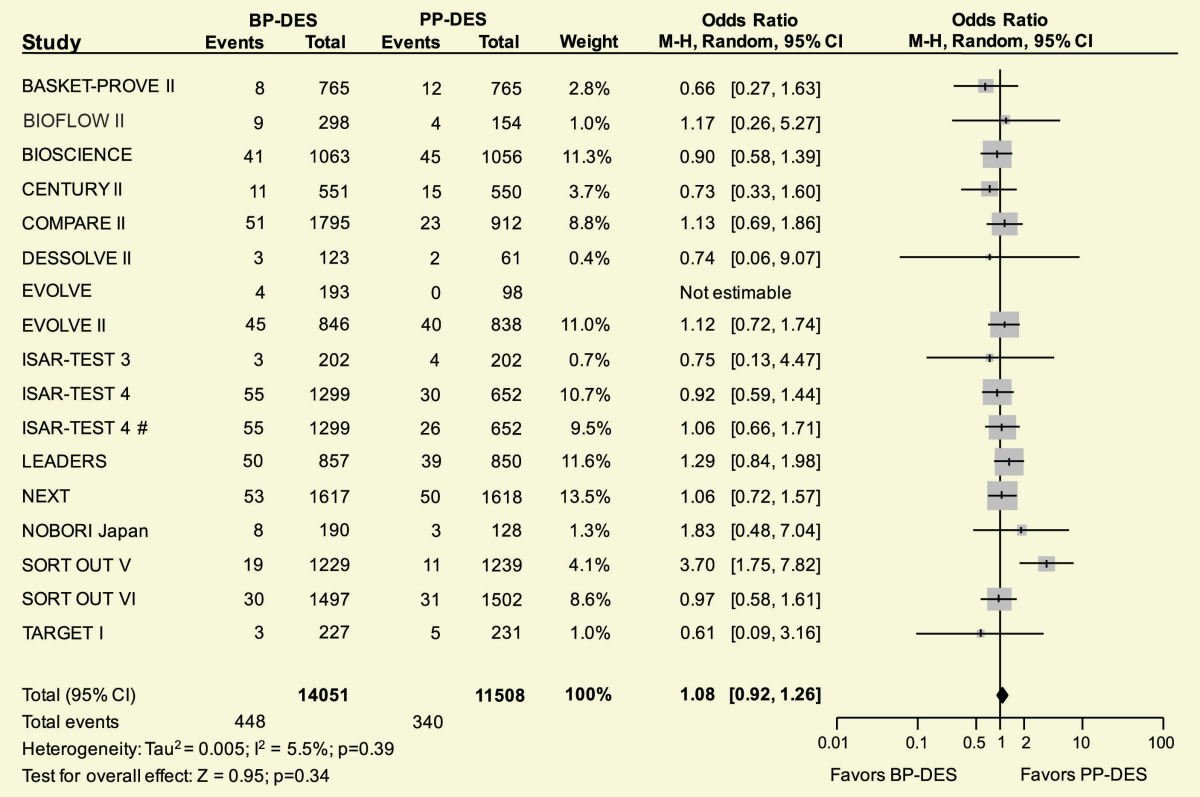

Abb. 23: Metaanalyse der Assoziation zwischen der Einjahres-Myokardinfarkt-Rate und der Therapie mit drug-eluting Stents (DES) mit biodegradierbaren Polymeren (BP-DES) gegen DES mit persistierenden Polymeren (PP-DES) [M]. BASKET-PROVE II trial = Safety and Efficacy Study Comparing 3 New Types of Coronary Stents[43], BIOFLOW II trial = Study of the Orsiro Drug Eluting Stent System[44], BIOSCIENCE trial = Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents[45], CENTURY II trial = Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease[46], COMPARE II trial = Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent[47], DESSOLVE II trial = Clinical Investigation of the MiStent DES in Coronary Artery Disease [8], EVOLVE and EVOLVE II trials = Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s)[49,50], ISAR-TEST 3 trial = Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis[51], ISAR-TEST 4 trial = 3 Limus Agent Eluting Stents With Different Polymer Coating[52], LEADERS trial, Limus Eluted From a Durable Versus Erodable Stent Coating[53], NEXT trial, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial[54], NOBORI Japan trial = Nobori Biolimus A9-Eluting Stent versus Sirolimus-Eluting Stent in Patients With Stenosis in Native Coronary Arteries[55], SORT-OUT V trial = Randomised Clinical Comparative Study of the Nobori and the Cypher Stent[56], SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity Stents[57]. TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V[58].

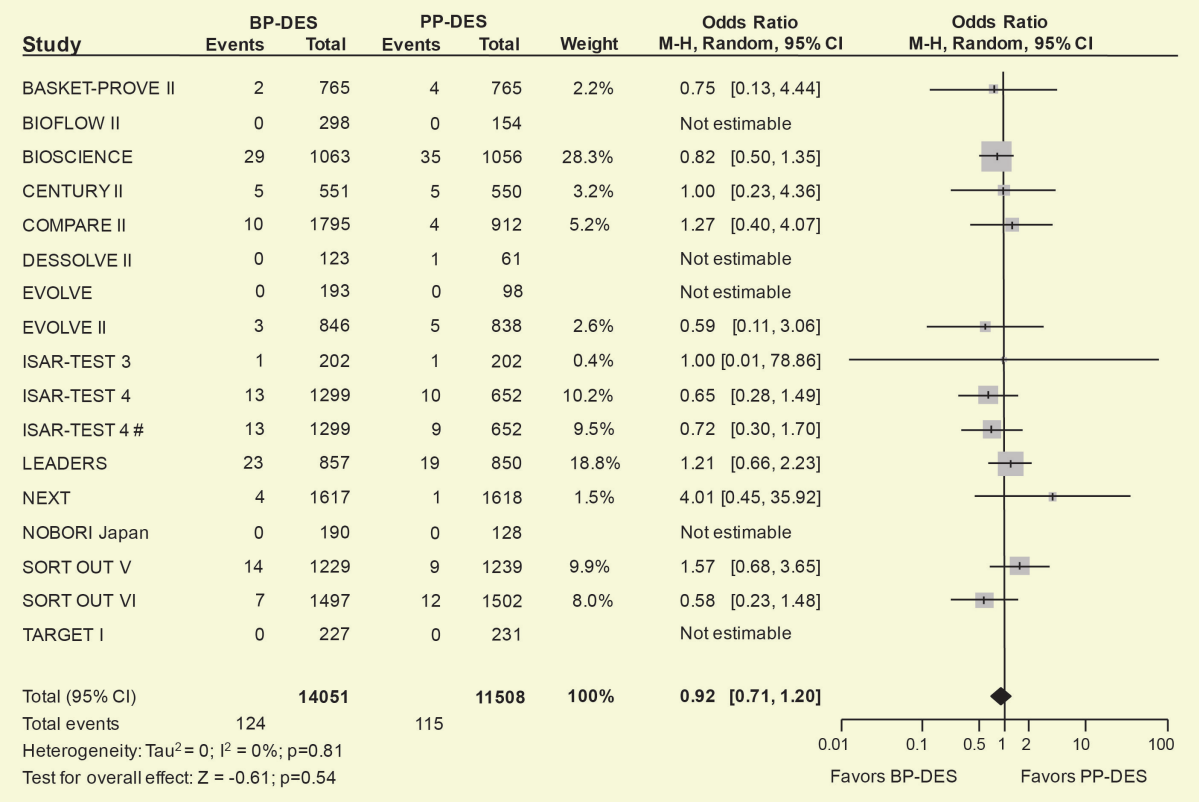

Abb. 24: Metaanalyse der Assoziation zwischen der Einjahres-Stentthrombose-Rate und der Therapie mit drug-eluting Stents (DES) mit biodegradierbaren Polymeren (BP-DES) gegen DES mit persistierenden Polymeren (PP-DES) [M]. BASKET-PROVE II trial = Safety and Efficacy Study Comparing 3 New Types of Coronary Stents[43], BIOFLOW II trial = Study of the Orsiro Drug Eluting Stent System[44], BIOSCIENCE trial = Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents[45], CENTURY II trial = Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease[46], COMPARE II trial = Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent[47], DESSOLVE II trial = Clinical Investigation of the MiStent DES in Coronary Artery Disease[48], EVOLVE and EVOLVE II trials = Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s)[49,50], ISAR-TEST 3 trial = Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis[51], ISAR-TEST 4 trial = 3 Limus Agent Eluting Stents With Different Polymer Coating[52], LEADERS trial, Limus Eluted From a Durable Versus Erodable Stent Coating[53], NEXT trial, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial[54], NOBORI Japan trial = Nobori Biolimus A9-Eluting Stent versus Sirolimus-Eluting Stent in Patients With Stenosis in Native Coronary Arteries[55], SORT-OUT V trial = Randomised Clinical Comparative Study of the Nobori and the Cypher Stent[56], SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity Stents[57]. TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V[58].

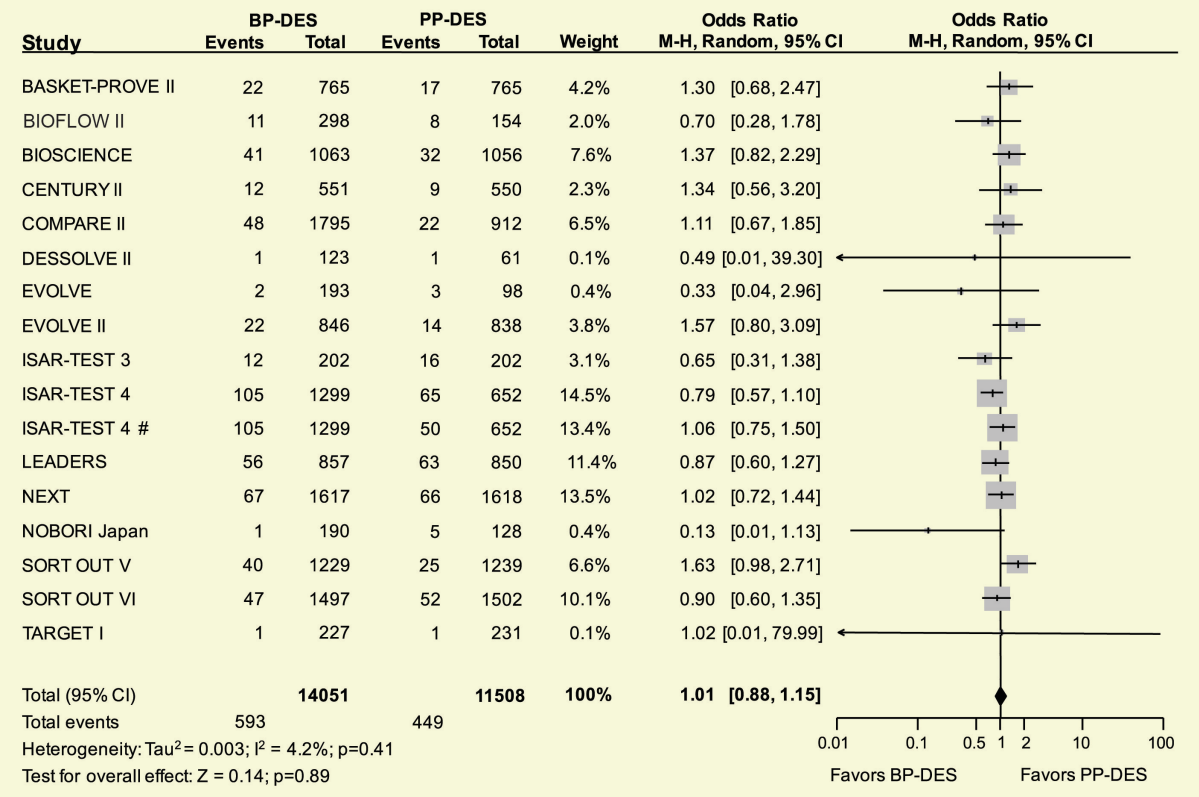

Abb. 25: Metaanalyse der Assoziation zwischen der Einjahres-Revaskularisations-Rate und der Therapie mit drug-eluting Stents (DES) mit biodegradierbaren Polymeren (BP-DES) gegen DES mit persistierenden Polymeren (PP-DES) [M]. BASKET-PROVE II trial = Safety and Efficacy Study Comparing 3 New Types of Coronary Stents[43], BIOFLOW II trial = Study of the Orsiro Drug Eluting Stent System[44], BIOSCIENCE trial = Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents[45], CENTURY II trial = Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease[46], COMPARE II trial = Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent[47], DESSOLVE II trial = Clinical Investigation of the MiStent DES in Coronary Artery Disease[48], EVOLVE and EVOLVE II trials = Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s)[49,50], ISAR-TEST 3 trial = Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis[51], ISAR-TEST 4 trial = 3 Limus Agent Eluting Stents With Different Polymer Coating[52], LEADERS trial, Limus Eluted From a Durable Versus Erodable Stent Coating[53], NEXT trial, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial[54], NOBORI Japan trial = Nobori Biolimus A9-Eluting Stent versus Sirolimus-Eluting Stent in Patients With Stenosis in Native Coronary Arteries[55], SORT-OUT V trial = Randomised Clinical Comparative Study of the Nobori and the Cypher Stent[56], SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity Stents[57]. TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V[58].

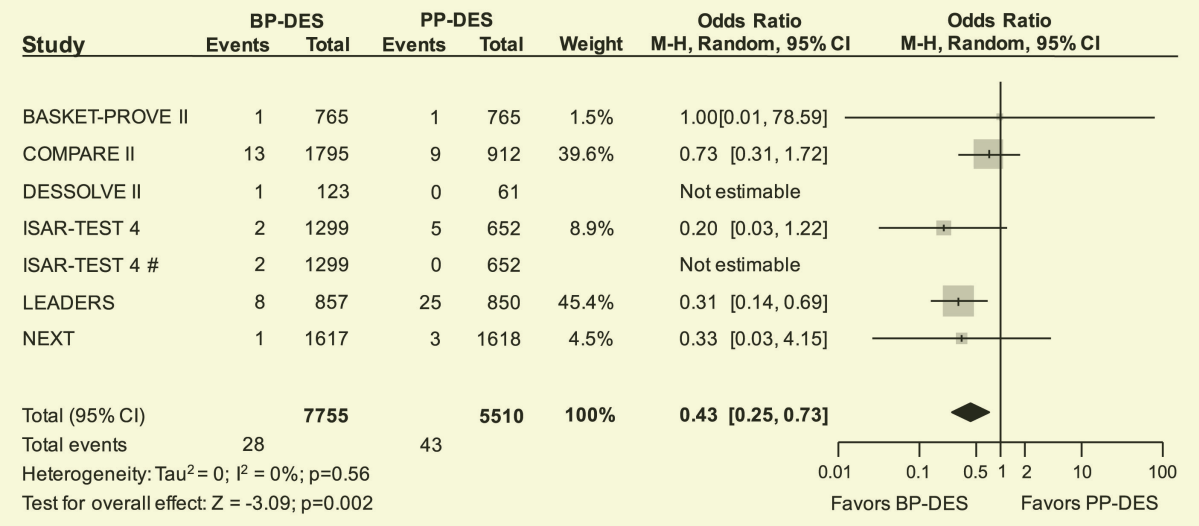

Abb. 26: Metaanalyse der Assoziation zwischen der späten Stentthrombose-Rate und der Therapie mit drug-eluting Stents (DES) mit biodegradierbaren Polymeren (BP-DES) gegen DES mit persistierenden Polymeren (PP-DES) [M]. BASKET-PROVE II trial = Safety and Efficacy Study Comparing 3 New Types of Coronary Stents[43], COMPARE II trial = Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent[59], DESSOLVE II trial = Clinical Investigation of the MiStent DES in Coronary Artery Disease[60], ISAR-TEST 4 trial = 3 Limus Agent Eluting Stents With Different Polymer Coating[61], LEADERS trial, Limus Eluted From a Durable Versus Erodable Stent Coating[62], NEXT trial, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial[63].

8. Diskussion und Zusammenfassung

Die Mortalität bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung bleibt trotz Weiterentwicklung der medikamentösen und interventionellen Therapie hoch. Die aktuellen Leitlinien empfehlen die primärprophylaktische Implantation eines Defibrillators bei Patienten mit reduzierter linksventrikulärer Auswurffraktion (LVEF ≤ 35%), welche derzeit als Goldstandard in der Risikoprädiktion gilt[10]. Die Sensitivität und Spezifität der LVEF in ist allerdings sehr beschränkt. Etwa 70% der Todesfälle nach einem Myokardinfarkt ereignen sich in der Patientengruppe mit erhaltener oder nur moderat eingeschränkter Pumpfunktion[11]. In der Patientengruppe mit hochgradig eingeschränkter LVEF, die mit ICD versorgt werden, erhält innerhalb von 5 Jahren nur jeder dritte Patient eine adäquate ICD-Therapie[12]. In einer vor kurzem veröffentlichten randomisierten Studie konnte an über 1.100 Patienten gezeigt werden, dass die ICD-Implantation das Sterberisiko bei Patienten mit nicht-ischämisch bedingter Kardiomyopathie und LVEF ≤35% nicht signifikant gesenkt hat[64]. Aus diesen Gründen sind neue Verfahren zur Risikostratifizierung von großer klinischer Bedeutung. Das Vorhandensein einer autonomen Dysfunktion des Herzens liefert prognostische Informationen, die von der LVEF unabhängig sind[14]. Darüber hinaus gibt es starke Evidenz, dass der Verlust vagaler Aktivität oder ein Übermaß sympathischer Aktivität mit einer schlechten Prognose vergesellschaftet sind.

Die Dezelerationskapazität des Herzens ist ein neues Maß der Herzfrequenzvariabilität, das die vagale Innervierung des Herzens auf der Ebene des Sinusknotens quantifiziert. In dieser Arbeit konnte gezeigt werden, dass DC ein signifikanter Mortalitätsprädiktor bei Patienten mit ischämischer Kardiomyopathie [B] und struktureller Herzerkrankung war [J]. Der Einsatz der DC in der medizinischen Notaufnahme führte zur Identifizierung von Hochrisikopatienten, die bei aktuellen Methoden nicht erfasst werden konnten [C,D]. Diese Ergebnisse unterstreichen die Wichtigkeit der Testung der autonomen Funktion in der Notaufnahme, die zur Verbesserung der aktuell verfügbaren Triagesysteme beitragen kann.

Periodic Repolarization Dynamics ist ein neues elektrokardiographisches Phänomen, das die sympathische Aktivität auf der Ebene des Ventrikelmyokards erfasst. In drei großen Kohorten war PRD ein starker Prädiktor der Gesamt-, sowie der kardiovaskulären Mortalität bei Patienten mit ischämischer Kardiomyopathie [E,H].

In der MADIT-II Studie[8], eine der wichtigsten Studien in der Kardiologie, die zur Etablierung der primärprophylaktischen ICD-Implantation bei Postinfarktpatienten mit hochgradig eingeschränkter LVEF als Grad-1-Empfehlung führte[10], war PRD einer der stärksten Prädiktoren der Gesamtmortalität, der kardiovaskulären Mortalität, des plötzlichen, sowie des nicht-plötzlichen Herztodes. Anhand von PRD konnten in der MADIT-II Studie neue Gruppen definiert werden, die von der primärprophylaktischen ICD-Implantation besonders oder nicht profitieren [H].

Die Kombination aus der DC als Marker des Verlustes vagaler Aktivierung und der PRD als Übermaß der sympathischen Aktivierung kann Patienten mit einem kardialen autonomen Versagen identifizieren [I]. In der Patientengruppe mit leichtgradig oder moderat eingeschränkter LV-Funktion (LVEF 35–50%) definieren die abnormale PRD oder DC eine neue Hochrisikogruppe, deren Prognose sich nicht von der von Patienten mit eingeschränkter LV-Funktion (LVEF ≤35%) unterscheidet. Diese Patientengruppe, die zahlenmäßig der Hochrisikogruppe mit LVEF ≤35% entspricht, bleibt in aktuellen Leitlinien jedoch unberücksichtigt. SMART-MI ist eine aktuell laufende prospektive, randomisierte, kontrollierte Studie, die Post-Infarktpatienten mit LVEF 35–50% auf eine kardiale autonome Dysfunktion testet. Patienten mit erhöhter PRD oder eingeschränkter DC sind als Risikopatienten betrachtet und werden 1:1 auf die Implantation eines Ereignisrekorders mit telemetrischer Überwachung oder eine konventionelle Therapie randomisiert. Entdeckt man vordefinierte Arrhythmien, so erfolgt eine spezifische Intervention im Sinne eines multifaktoriellen Ansatzes [L]. Dies kann z.B. eine orale Antikoagulation im Fall von Vorhofflimmern oder eine Ischämiediagnostik im Fall von nicht-anhaltenden ventrikulären Tachykardien bedeuten. Bei höhergradigen AV-Blockierungen kann eine Schrittmacherimplantation indiziert sein, bei anhaltenden ventrikulären Tachykardien eine Ablation oder eine ICD-Implantation.

Zusammenfassend konnten in dieser Arbeit anhand der kardialen autonomen Dysfunktion neue Ansätze zur Risikostratifizierung bei Patienten mit ischämischer Kardiomyopathie und struktureller Herzerkrankung untersucht werden. Diese Ansätze führten zur Identifizierung von Hochrisikopatienten, die bei den gegenwärtigen Methoden nicht erfasst werden können. Eine Biomonitoring-gesteuerte, personalisierte Therapie bei diesen Hochrisikopatienten mit autonomer Dysfunktion könnte ein vielversprechender neuer Therapieansatz sein.

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10. Veröffentlichungen zum Thema als Erst-,Letzt- und Coautor

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B. Rizas KD, Eick C, Doller AJ, Hamm W, Stuelpnagel von L, Zuern CS, Barthel P, Schmidt G, Bauer A. Bedside autonomic risk stratification after myocardial infarction by means of short-term deceleration capacity of heart rate. *Europace* 2017 (In Press)

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D. Eick C, Duckheim M, Groga-Bada P, Klumpp N, Mannes S, Zuern CS, Gawaz M, **Rizas KD**[*], Bauer A[*]. Point-of-care testing of cardiac autonomic function for risk assessment in patients with suspected acute coronary syndromes. *Clin Res Cardiol* Springer Berlin Heidelberg; 2017;163:1–9.

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G. Rizas KD, Bauer A. [Periodic Repolarization Dynamics - innovative strategies for preventing sudden death]. *Dtsch Med Wochenschr*, Georg Thieme Verlag KG; 2016;141:504–508.

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K. Rizas KD, Zuern CS, Bauer A. Periodic repolarization dynamics in patients with moderate to severe aortic stenosis. *J Electrocardiol* 2017;50:802–807.

L. Hamm W, **Rizas KD**, Stülpnagel LV, Vdovin N, Massberg S, Kääb S, Bauer A. Implantable cardiac monitors in high-risk post-infarction patients with cardiac autonomic dysfunction and moderately reduced left ventricular ejection fraction: Design and rationale of the SMART-MI trial. *Am Heart J* 2017;190:34–39.

M. Rizas KD, Mehilli J. Stent Polymers: Do They Make a Difference? *Circ Cardiovasc Interv* Lippincott Williams & Wilkins; 2016;9:e002943.

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11. Danksagung

An erster Stelle möchte ich mich ganz herzlich bei Herrn Professor Dr. med. Axel Bauer, meinem wissenschaftlichen Ziehvater, Herrn Professor Dr. med. Steffen Massberg, Direktor der Medizinischen Klinik und Poliklinik I am Klinikum der Universität München, sowie bei meinem ehemaligen Chef Herrn Professor Dr. med. Meinrad Gawaz, Direktor der Medizinischen Klinik III am Universitätsklinikum Tübingen bedanken, die mir meine wissenschaftlichen Arbeiten auf dem Gebiet der klinischen Kardiologie und Elektrophysiologie ermöglicht haben. Ihre stete Förderung und Unterstützung sind der Grundstein der vorliegenden Arbeit. Ein besonderer Dank gilt auch Herrn Professor Dr. med. Georg Schmidt, welcher mich bei allen kooperativen Projekten unterstützt hat.

Letztendlich möchte ich mich bei meiner gesamten Familie bedanken, die mir immer zur Seite standen und mich auch in schwierigen Phasen unterstützt haben. Herauszuheben ist meine liebe Frau, Alexia, die mich angetrieben hat, um diese Arbeit erfolgreich fertigzustellen, vor allem im harten Endspurt.

12. Lebenslauf

1.1 Persönliche Daten

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1.2 Schul- und Hochschulausbildung

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1.3 Berufliche Ausbildung und Klinischer Werdegang

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11/2017 – heute	Funktionsoberarzt, Medizinische Klinik I, Klinikum der Universität München (Prof. Dr. med. S. Massberg)

1.4 Wissenschaftlicher Werdegang

2010 – heute	Arbeitsgruppe für Biosignalanalyse, medizinische Klinik III, Universitätsklinikum Tübingen und medizinische Klinik I, Klinikum der Universität München (Prof. Dr. A. Bauer)
2011	Promotion zum Dr.med. ("*magna cum laude*") mit dem Thema: *„T-Wave Rhythmicity as a predictor of mortality after myocardial infarction",* Eberhard Karls Universität Tübingen
2008 – 2009	Arbeitsgruppe für die Pathogenese des abdominellen Aortenaneurysmas (Prof. M. Tilson, Columbia university, NY)

1.5 Mitgliedschaft in Fachgesellschaften

Seit 2016	Deutsche Gesellschaft für Kardiologie (DGK)
Seit 2016	Mitglied der Europäischen Gesellschaft für Kardiologie
Seit 2016	Deutsches Zentrum für Herzkreislaufforschung (DZHK)
Seit 2017	European Heart Rhythm Association (EHRA)
Seit 2017	Fellow der Europäischen Gesellschaft für Kardiologie

1.6 Preise und Auszeichnungen

2013	Young Investigator Award “Clinical Science”

1.7 Lehrtätigkeit

SS 2010 – WS 2013/2014	EKG-Kurs und Bedside Teaching Kardiovaskuläres System (Eberhard Karls Universität Tübingen)
Seit SS 2014	Bedside Teaching Kardiovaskuläres System und Seminar Kardiovaskuläres System (Klinikum der Universität München)

1.8 Betreuung von Doktoranden

2015	Doller, AJ. Bedside Autonomic Risk Stratification after Myocardial Infarction by means of Deceleration Capacity of Heart Rate. Unpublished thesis
2016	Kerschl, J. Risk stratification in patients with Long-QT Syndrome by means of Periodic Repolarization Dynamics. Unpublished thesis
2017	Wenner, F. Normal values of heart rate variability in healthy individuals. Unpublished thesis

1.9 Wissenschaftliche Gutachtertätigkeit

Seit 2013	Pacing and Clinical Electrophysiology
Seit 2014	Europace
Seit 2017	Journal of Electrocardiology

1.10 Sprachen / Programmiersprachen

Sprachen	Griechisch (Muttersprache) Deutsch (Verhandlungssicher) Englisch (Verhandlungssicher)
Programmiersprachen	HTML, Ajax, Flash, PHP, MySQL, Java, Objective C, Matlab, CRAN R Statistics

1.11 Kongressvorträge

02/2009	Academic Surgical Congress 2009 *Multilayer genomic analysis of mitochondrial DNA in patients with AAA using a novel web application*
04/2012	78. Jahrestagung der DGK *Effects of sequential autonomic activation and blockade on deceleration capacity of heart rate in the swine model*
04/2013	79. Jahrestagung der DGK *Schwere autonome Dysfunktion als Risikoprädiktor bei Patienten mit höhergradiger Aortenklappenstenose, die einen Aortenklappenersatz erhalten*
08/2013	ESC Congress 2013 (Young Investigator Award) *Low Frequency Waves of Repolarization - A novel predictor of mortality after myocardial infarction.*
04/2015	81. Jahrestagung der DGK *Increased resting level of periodic repolarization dynamics predicts exercise-induced T-wave alternans.*

04/2016	82. Jahrestagung der DGK *Periodic Repolarization Dynamics quantified by Phase-Rectified-Signal-Averaging is a strong and robust predictor of mortality after myocardial infarction.*
08/2016	ESC Congress 2016 *Assessment of deceleration capacity from short-term recordings predicts mortality after myocardial infarction: Prospective validation study.*
08/2016	ESC Congress 2016 *Risk stratification after myocardial infarction based on Periodic Repolarization Dynamics - Impact of gender and diabetes mellitus and clinical implications.*
08/2016	ESC Congress 2016 *Periodic repolarization dynamics quantified by phase-rectified-signal-averaging - A strong and robust predictor of mortality after MI*
09/2016	EU-CERT-ICD General Assembly Meeting Barcelona *Periodic Repolarization Dynamics and its clinical applications*
04/2017	*42nd ISCE Congress* *Periodic Repolarization Dynamics and its clinical implications.*
08/2017	ESC Congress 2017 *Periodic Repolarization Dynamics as risk predictor after myocardial infarction - PRD-MI prospective validation study.*
08/2017	ESC Congress 2017 *Periodic Repolarization Dynamics as risk predictor in patients with Long-QT Syndrome.*

München, 28.11.2017

Dr. med. Konstantinos Rizas

13. Sonderdrucke der kumulativen Habilitation

Europace Advance Access published October 1, 2012

Europace
doi:10.1093/europace/eus323

EDITORIAL

Risk stratification after myocardial infarction: it is time for intervention

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Received 13 August 2012; accepted after revision 30 August 2012

This editorial refers to 'Non-invasive risk stratification for sudden cardiac death by heart rate turbulence and microvolt T-wave alternans in patients after myocardial infarction' by V. Sulimov *et al.*, doi:10.1093/europace/eus238

Despite significant advances in interventional and pharmacological therapies, late mortality after acute myocardial infarction (MI) is still high. Approximately 50% of cardiovascular deaths after MI occur suddenly and are potentially preventable by prophylactic implantation of a cardioverter-defibrillator (ICD). In recent decades, substantial efforts have been made to identify high-risk patients who may benefit from prophylactic therapy. While initial risk stratification strategies guiding ICD therapy were based on the comprehensive electrophysiological testing in highly selected subgroups of patients, a revolutionary concept was proposed in 2002, when Moss *et al.*[1] presented the results of MADIT-2 (Multicentre Automatic Defibrillator Implantation Trial). In contrast with all previous attempts, MADIT-2 used the finding of a reduced left ventricular ejection fraction (LVEF) as the single selection criterion for prophylactic ICD-implantation. In terms of efficacy and effectiveness, the MADIT-2 criterion was a great success. Subsequent trials confirmed the concept of prophylactic ICD-implantation in patients with impaired LVEF, and later economic analyses verified the cost-effectiveness of this approach.

However, when looking from an epidemiological point of view at the global impact of ICD on the disease burden of sudden cardiac death (SCD) after MI, there is a growing sense of disillusionment. The vast majority of post-MI patients prone to SCD are not captured by the MADIT-2 criterion, and die despite exhibiting preserved or only moderately impaired LVEF.[2] Identifying high-risk individuals after MI by reduced LVEF is therefore like looking at the tip of an iceberg with a telescope. Several studies have documented that the sensitivity of impaired LVEF in predicting death after MI is as poor as 30%; it is unlikely that a diagnostic test with such a low sensitivity would be accepted in many other fields of modern medicine.

But what are the alternatives? In the current issue of the *Journal*, Sulimov *et al.*[3] report on the usefulness of the combination of two electrocardiogram (ECG)-based risk predictors, heart rate turbulence (HRT), and microvolt T-wave alternans (TWA), for the prediction of SCD after MI. Heart rate turbulence quantifies the baroreflex-mediated short-term oscillation of cardiac cycle lengths following spontaneous ventricular premature complexes.[4] T-wave alternans refers to the beat-to-beat fluctuation in the morphology and amplitude of the ST segment and/or T-wave related to instabilities in membrane voltage and disruptions in intracellular calcium cycling dynamics.[5] The combination of both markers makes sense from a pathophysiological point of view, as they capture different pathologies involved in the genesis of SCD. The main finding of the study was that both HRT and TWA were strong and independent predictors of SCD, yielding relative risks of 12.4 and 5.0, respectively. However, the study is limited in several respects. First, the study is underpowered; a sample size of 111 patients (out of whom 15 reached the primary endpoint of SCD) is too small by orders of magnitude to address the question of interest. Second, cumulative 1-year event rates of SCD were surprisingly high (13.5%). For comparison, in the 14 609 participants in the VALLIANT (VALsartan In Acute myocardial iNfarcTion) study, this figure was as low as 5.1%.[6] Third, several technical and statistical issues remain, as the authors used a non-standard ECG lead configuration and defined new cut-off values for TWA that require prospective validation.

Nevertheless, the limitations of the study by Sulimov *et al.* do not necessarily imply that the conclusions are wrong. There is a huge body of evidence from retrospective and prospective studies (together including more than 10 000 patients) that both HRT and TWA are powerful predictors of risk after MI (*Figure 1*). The combination of HRT and TWA was also tested in the REFINE (Risk Estimation Following Infarction Noninvasive Evaluation) study.[7] Of particular importance, both predictors are useful for the identification of high-risk patients otherwise classified as low-risk, making both markers suitable for combination

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

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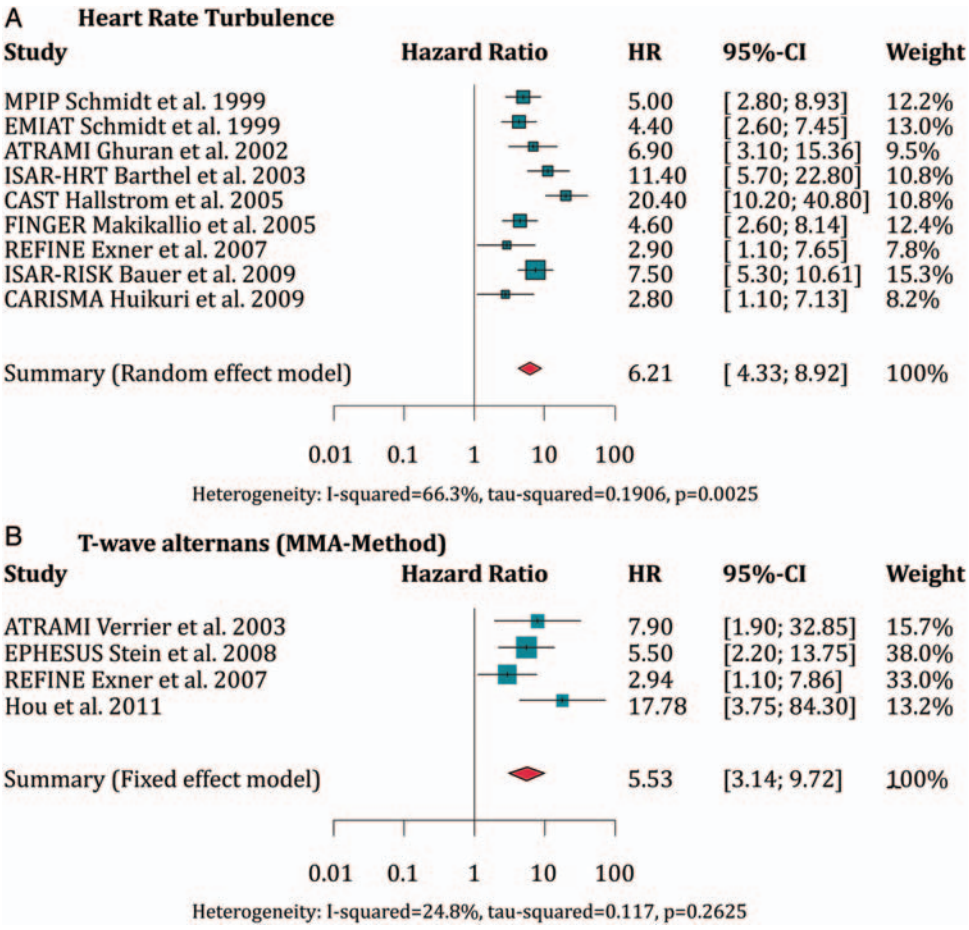

Figure 1 Meta-analyses of clinical trials testing heart rate turbulence (*A*) and T-wave alternans (assessed by the modified moving average method which has been used in the article by Sulimov *et al.*) (*B*) as predictors of mortality in post-myocardial infarction patients. Details of and references to the single studies can be found elsewhere.[4,5] For meta-analysis of heart rate turbulence, we used a random effects model to address significant heterogeneity among the single studies. For meta-analysis of T-wave alternans, we used a fixed model due to non-significant heterogeneity in single studies.

with established criteria.[4,5] The positive predictive values and specificities of both markers are in the range of that provided by impaired LVEF, suggesting that ICD may be equally effective.[8,9] As is the case with many other methods, HRT and TWA have several shortcomings that are beyond the scope of this editorial but do not affect the risk-predictive power of both methods. Given this information, why have none of these markers been tested in a randomized, interventional ICD trial?

Although several reasons could be cited here, the central question remains: who is going to pay for such a trial? The costs of a prospective, multicentre ICD trial are enormous, and probably could only be covered by large ICD companies. However, these companies need to follow the rules of economy, balancing the potential benefits of widened ICD indications against the associated costs and, importantly, the risks of a negative outcome. In this respect, the DINAMIT (Defibrillation in Acute Myocardial Infarction Trial)[10] and IRIS (Immediate Risk-Stratification Improves Survival)[8] studies, which addressed questions different from those proposed here, were painful experiences for St Jude Medical and Medtronic. While discussing expansions of ICD indications to fight SCD, it is important to note that ICD therapy is still significantly underused in most, if not all, European countries according to already approved criteria.[9] Nonetheless, as scientists we should promote the prospective validation of sound concepts. We strongly believe that prophylactic ICD in high-risk post-MI patients characterized by abnormal HRT and/or TWA belongs to this category of concepts.

Conflicts of interest: none.

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Europace (2017) **0**, 1–8
doi:10.1093/europace/eux167

CLINICAL RESEARCH

Bedside autonomic risk stratification after myocardial infarction by means of short-term deceleration capacity of heart rate

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Received 4 April 2017; editorial decision 19 April 2017; accepted 24 April 2017

Aims Twenty-four-hour deceleration capacity (DC_{24h}) of heart rate is a strong predictor of mortality after myocardial infarction (MI). Assessment of DC from short-term recordings (DC_{st}) would be of practical use in everyday clinical practice but its predictive value is unknown. Here, we test the usefulness of DC_{st} for autonomic bedside risk stratification after MI.

Methods and results We included 908 patients after acute MI enrolled in Munich and 478 patients with acute ($n = 232$) and chronic MI ($n = 246$) enrolled in Tuebingen, both in Germany. We assessed DC_{st} from high-resolution resting electrocardiogram (ECG) recordings (<30 min) performed under standardized conditions in supine position. In the Munich cohort, we also assessed DC_{24h} from 24-h Holter recordings. Deceleration capacity was dichotomized at the established cut-off value of ≤ 2.5 ms. Primary endpoint was 3-year mortality. Secondary endpoint was 3-year cardiovascular mortality. In addition to DC, multivariable analyses included the Global Registry of Acute Coronary Events score >140 and left ventricular ejection fraction ≤ 35%. During follow-up, 48 (5.3%) and 48 (10.0%) patients died in the Munich and Tuebingen cohorts, respectively. On multivariable analyses, $DC_{st} \leq 2.5$ ms was the strongest predictor of mortality, yielding hazard ratios of 5.04 (2.68–9.49; $P < 0.001$) and 3.19 (1.70–6.02; $P < 0.001$) in the Munich and Tuebingen cohorts, respectively. Deceleration capacity assessed from short-term recordings ≤ 2.5 ms was also an independent predictor of cardiovascular mortality in both cohorts. Implementation of $DC_{st} \leq 2.5$ ms into the multivariable models led to a significant increase of C-statistics and integrated discrimination improvement score.

Conclusion Deceleration capacity assessed from short-term recordings is a strong and independent predictor of mortality and cardiovascular mortality after MI, which is complementary to existing risk stratification strategies.

Keywords Deceleration capacity of heart rate • Heart rate variability • Myocardial infarction • Risk stratification • Short-term electrocardiogram recordings

Introduction

Risk stratification after myocardial infarction (MI) is of crucial importance to guide preventive strategies. Reduced left ventricular ejection fraction (LVEF ≤ 35%) remains the current gold standard risk predictor.[1] However, it lacks both sensitivity and specificity.[2] In fact, the majority of patients who die after MI have an LVEF of 36% or

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What's new?

- Twenty-four-hour deceleration capacity (DC_{24h}) of heart rate is a strong predictor of mortality after myocardial infarction. However, the need of 24-h recordings is considered as major drawback. Here, we tested the usefulness of deceleration capacity assessed from short-term recordings (DC_{st}) in two large cohorts.
- In both cohorts, DC_{st} was the strongest predictor of 3-year mortality.
- Deceleration capacity assessed from short-term recordings was independent from established risk predictors including the Global Registry of Acute Coronary Events score and left ventricular ejection fraction (LVEF).
- The predictive value of DC assessed from short-term recordings was comparable to that of DC assessed from 24-h recordings.
- Deceleration capacity assessed from short-term recordings is a useful tool for bedside risk stratification that complements LVEF and clinical factors.

greater,[2–4] highlighting the need for refined risk stratification strategies.

Deceleration capacity (DC) of heart rate is an advanced marker of heart rate variability (HRV) that yields strong and independent prognostic information in post-infarction patients.[5] Deceleration capacity is an integral measure of all deceleration-related oscillations of heart rate over 24 h, including regulations in the ultra-low, very low, low, and high frequency bands. In previous studies, the prognostic value of impaired DC in predicting late mortality after MI exceeded that of abnormal standard measures of HRV and even reduced LVEF.[5]

However, in the light of increasingly shorter hospital stays the need of a full 24-h Holter recording for DC assessment is considered as a major drawback. For practical reasons, bedside autonomic risk stratification that could be performed in a comparable time frame as the echocardiographic assessment of left ventricular function would be greatly appreciated and would help implementing autonomic risk stratification in everyday clinical practice. In addition, compared to 24-h recordings, short-term ECGs can be performed under standardized conditions eliminating noise, artifacts, and non-stationarities.

We therefore undertook this study to test the usefulness of DC obtained from short-term ECG-recordings (DC_{st}) in predicting death after MI.

Methods

Study design and study populations

The prognostic value of DC_{st} was evaluated in two post-infarction cohorts, the Munich and Tuebingen cohort.

The study design of the Munich cohort has been described elsewhere[6] and is illustrated in *Figure 1A*. The study included 908 survivors of acute MI (left column of *Table 1*). Patients were enrolled between May 2000 and March 2005 at two university centres in Munich, Germany, the German Heart Centre and the Klinikum Rechts der Isar. Eligible patients had survived an acute MI (≤40 days), were aged ≤80 years, had sinus rhythm, and did not meet the criteria for prophylactic ICD implantation prior hospital discharge.

Patients of the Tuebingen cohort were prospectively enrolled between September 2010 and February 2014 at the university hospital of Tuebingen, Germany (*Figure 1B*). Inclusion criteria consisted of history of previous MI, sinus rhythm and age ≤80 years [$n = 478$, median age 66 (IQR 17), 109 females (22.8%); right column of *Table 1*]. Compared with the Munich cohort, the study was not limited to patients with acute MI. In 246 of the patients (51.5%), the index MI was older than 40 days. The ethics committees of Munich and Tuebingen approved both studies.

Procedures

In both cohorts, high-resolution digital ECGs (Munich cohort: TMS, Porti System version 1; 1600 Hz; 30 min; Tuebingen cohort: TMS, Porti System version 2; 2048 Hz; 20 min) were performed in Frank leads configuration. The recordings were done in the morning hours under standardized conditions in supine and resting position. Patients were spontaneously breathing. In the Munich cohort, the median time from the index MI to the ECG recording was 7 (IQR 4) days. In Tuebingen cohort, which also included patients with chronic MI, the median time from the index MI to the ECG recording was 154 (IQR 3071) days.

In the Munich cohort, additionally, 24-h Holter recordings (Oxford Excel Holter system, Oxford instruments; Pathfinder700, Reynolds Medical; and Mortara Holter system, Mortara Instrument) were performed in 861 patients within the second week after MI.

Assessment of deceleration capacity

Deceleration capacity assessed from short-term recordings and DC_{24h} were calculated using the same algorithms.[5,7] The exact technology of DC assessment has been described elsewhere. Very briefly, computation of DC is based on the transformation of the sequence of RR intervals into a new time series by phase-rectified signal averaging (PRSA). In a first step, RR intervals that are longer than their respective preceding RR-intervals are identified (so-called anchors). In a second step, segments around anchors are averaged to obtain the so-called PRSA-signal. The PRSA-signal can be considered as a condensed version of the original RR-interval time series, including all periodic components of HRV related to decelerations. The central part of the PRSA-signal is quantified by wavelet-analysis to obtain the numerical measure of DC (*Figure 2*). Thus, DC is an integral measure of all deceleration-related oscillations that take place during the observational period. As previously described, patients with DC ≤ 2.5 ms were classified as high-risk patients.

Assessment of other risk predictors

Left ventricular ejection fraction was assessed by echocardiography or angiography. The Global Registry of Acute Coronary Events (GRACE) score was calculated as previously described[8] and included following variables: age, heart rate, systolic blood pressure, creatinine level, Killip class, cardiac arrest at admission, ST-segment deviation, and elevated cardiac enzyme levels. The GRACE score was dichotomized at the established cut-off value of >140. Estimated glomerular filtration rate (eGFR) was estimated using the modified diet in renal disease formula and dichotomized at the cut-off value of <60 mL/min/1.73 m^2. To compare DC_{st} with standard measures of HRV,[9] all measures in time and frequency domain as well as non-linear indices were calculated according to the recommendations provided by the task force.[9] For each domain, we identified the measure that showed the strongest association with the primary endpoint in the Munich cohort. As no established cut-off values for short-term HRV measures exist, we used maximally selected rank statistics to

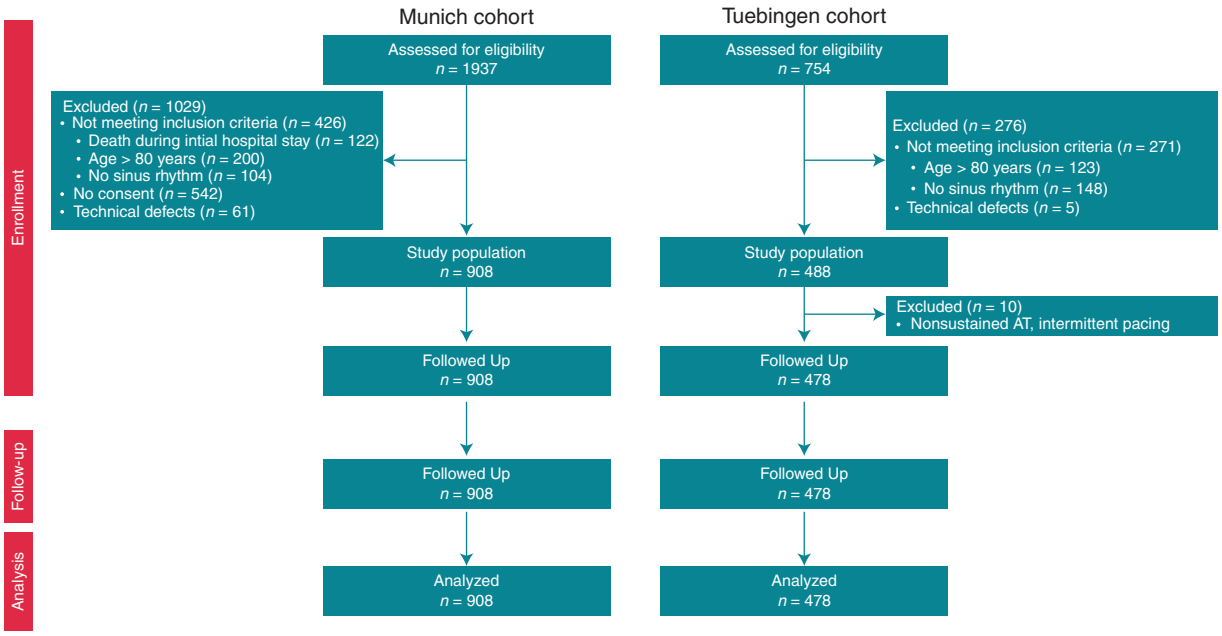

Figure 1 Consort flow-diagrams for the training and validation cohorts.

determine the optimum cut-off values for all markers, which were then also used in the Tuebingen cohort.

Study endpoints and follow-up

In both cohorts, primary endpoint was 3-year all-cause mortality. Secondary endpoint was 3-year cardiovascular mortality. Patients were followed-up at regular intervals, either in the outpatient clinic or by telephone calls, with median follow-up periods of 36 and 27 months, respectively.

Statistical analysis

Continuous variables are presented as medians with IQRs and were compared using the Wilcoxon rank-sum test. Categorical variables are expressed as percentages and were analysed using the χ^2 and Fisher's exact tests. We quantified receiver-operator characteristic (ROC) curves by the integrals of the curves (AUC, area under the curve), plotting the dependency of specificity on sensitivity. To test the difference between two ROC curves, we used bootstrapping, based on the creation of pseudo-replicate datasets by random resampling of the dataset *N* times for error estimation ($N = 2000$ in this study). We estimated survival curves using the Kaplan–Meier method and compared them by means of the log-rank test. Sensitivities and specificities were extracted from the survival curves. Multivariable analyses were implemented by the adaptation of Cox regression models. Subgroup analyses were performed by means of the regression technique. Results are presented as hazard ratios with 95% confidence interval (CI). To test the incremental prognostic value of DC_{st} on top of the GRACE score and LVEF, we implemented C-statistics, integrated discrimination improvement (IDI) score, and continuous net reclassification improvement analysis (NRI). To test the difference between C-statistics bootstrapping was employed. Agreement between DC_{st} with DC_{24h} was assessed by the method described by Bland and Altman. Differences were considered statistically significant when the two-sided *P*-value was less than 0.05. All statistical analyses were performed using CRAN R, version 3.2.3.

Results

Table 1 shows baseline, clinical, follow-up, and treatment characteristics in the Munich ($n = 908$) and Tuebingen cohorts ($n = 478$). In the Munich cohort, 48 patients died (27 cardiovascular deaths) during a median follow-up time of 36.0 months. In the Tuebingen cohort, 48 patients died (24 cardiovascular deaths) over a median interval of 27.3 months. Supplementary material online, *Table S1* shows association of clinical parameters with $DC_{st} \leq 2.5$ ms.

Figure 2 shows representative PRSA-signals from short-term recordings in two post-MI patients of the Munich cohort. *Panel A* shows a patient who survived the 3-year follow-up period. *Panel B* shows a patient who suddenly died 9 weeks after the index MI. In the surviving patient, the amplitude of the PRSA-signal is significantly higher as compared to the non-surviving patient.

Table 2 shows the association of risk factors with 3-year all-cause mortality. In both cohorts, non-surviving patients were older, had a lower LVEF and had higher GRACE scores. Non-surviving patients in the Munich cohort but not in the Tuebingen cohort had higher incidence of diabetes mellitus. In both cohorts, non-surviving patients had substantially lower DC_{st} compared to surviving patients (2.0 ± 3.6 vs. 4.8 ± 3.9 ms in the Munich cohort and 1.4 ± 3.5 vs. 4.1 ± 4.0 ms in the Tuebingen cohort, $P < 0.001$ for both).

Figure 3*A* and *B* depict cumulative mortality rates of patients stratified by $DC_{st} \leq 2.5$ ms in the Munich cohort and Tuebingen cohort, respectively. In the Munich cohort, the 182 patients with $DC_{st} \leq 2.5$ ms

Table 1 Patients', clinical, and treatment characteristics in the Munich and Tuebingen cohorts

Characteristic	Munich cohort	Tuebingen cohort
Study characteristics		
Number of patients, *n*	908	478
Median follow-up (IQR), months	36.0 (0)	27.3 (11.3)
Total deaths, *n*	48	48
Cardiovascular deaths, *n*	27	24
Patients' and clinical characteristics		
Age (IQR), years	61 (17)	66 (17)
Acute MI, *n* (%)	908 (100)	232 (48.6)
Acute MI localization (AW, LW, PW) (%)	42/11/47	46/19/35
Time from index MI, days (IQR)	7 (4)	154 (3071)
Females, *n* (%)	174 (19.2)	109 (22.8)
Diabetes mellitus, *n* (%)	179 (19.7)	210 (43.9)
LVEF, % (IQR)	53 (15)	50 (15)
GRACE, Score (IQR)	110 (32)	134 (43)
eGFR, mL/min/1.73 m^2 (IQR)	69 (25)	79 (32)
SP on admission, mmHg (IQR)	130 (35)	130 (27)
Cardiogenic shock on admission, *n* (%)	10 (1.1)	11 (2.3)
Previous MI, *n* (%)	86 (9.5)	277 (58)
Multivessel CAD, *n* (%)	563 (62.0)	387 (81)
MHR, bpm (IQR)	62 (13)	65 (16)
DC_{24h}, ms (IQR)	5.2 (3.5)	n/a
DC_{st}, ms (IQR)	4.7 (4.0)	3.9 (4.0)
Treatment		
PCI, *n* (%)	848 (93.4)	439 (92)
CABG surgery, *n* (%)	32 (3.5)	48 (10)
Beta-blockers, *n* (%)	864 (95.1)	440 (92.1)
Statins, *n* (%)	843 (92.8)	432 (90.4)
ACE Inhibitor	850 (93.6)	366 (76.6)

ACE, angiotensin converting enzyme; AW, anterior wall; CAD, coronary artery disease; DC_{st}, deceleration capacity assessed from short-term recordings; DC_{24h}, deceleration capacity assessed from 24-h Holter electrocardiograms; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; LVEF, left-ventricular ejection fraction; LW, lateral wall; MHR, mean heart rate from short-term recordings; MI, myocardial infarction; PCI, percutaneous coronary intervention; PW, posterior wall; SP, systolic pressure.

had a 3-year mortality rate of 16.5% compared to 3-year mortality rate of 2.5% in the 726 patients with $DC_{st} > 2.5$ ms (*Figure 3A*), corresponding to a sensitivity of 63% and specificity of 82%. Also in the Tuebingen cohort, risk stratification by $DC_{st} \leq 2.5$ ms led to highly significant separation of low and high-risk patients. The 152 patients with $DC_{st} \leq 2.5$ ms have a 3-year mortality rate of 27.5% compared to a 3-year mortality rate of 6.3% in the 326 patients with $DC_{st} > 2.5$ ms (*Figure 3B*), corresponding to a sensitivity of 67% and specificity of 73%.

In both cohorts, DC_{st} was the strongest predictor of mortality in uni- and multivariable Cox regression analyses (*Table 3* and Supplementary material online, *Table S2*). Its predictive value was independent from and incremental to that of the GRACE score and LVEF, as well as that of HRV-index (HRVI) ≤ 26 units, the normalized power in the low frequency range (LFn) ≤ 0.42, and the multiscale sample entropy index ≤ 4.47, which were the strongest HRV measures in the Munich cohort (*Table 3* and Supplementary material online, *Table S2*). Implementing DC_{st} into the multivariable model of GRACE score and LVEF led to a significant increase of C-statistics from 68.23% (95% CI 61.16–75.71%) to 76.80% (69.11–83.86%; $P = 0.004$ for difference) in the Munich cohort and from 70.16% (62.16–77.55%) to 76.83% (69.98–82.98%; $P = 0.017$ for difference) in the Tuebingen cohort. Integrated discrimination improvement increased by 0.045 (0.018–0.092, $P < 0.001$) in the Munich cohort and by 0.037 (0.006–0.110, $P = 0.007$) in the Tuebingen cohort, whereas continuous NRI improved by 0.449 (0.314–0.577, $P < 0.001$) in the Munich cohort and by 0.389 (0.214–0.558, $P < 0.001$) in the Tuebingen cohort. Deceleration capacity assessed from short-term recordings was also a strong and independent predictor of cardiovascular mortality in both cohorts (*Table 3*). Adjusting for other parameters, including treatment with beta-blockers and statins did not have a significant impact on the predictive power of DC_{st}.

In the Munich cohort, we also compared DC from short-term and 24-h recordings. DC_{24h} was slightly higher than DC_{st} (mean difference 0.62 ± 5.97, $P = 0.002$, Supplementary material online, *Figure S2*). The Pearson's correlation coefficient between the two measurements was 0.75 (0.72–0.78, $P < 0.001$). Univariable analysis revealed that both measurements yielded comparable AUC (73.37%, [64.28–81.67%] for DC_{st} and 76.24%, [67.75–83.85%] for DC_{24h}; $P = 0.386$ for the difference; Supplementary material online, *Figure S1*). However, in multivariable analysis including both DC_{st} and DC_{24h}, only DC_{st} was significantly associated with prediction of 3-year mortality (see Supplementary material online, *Table S3*).

Subgroup analyses revealed that DC_{st} was stronger predictor of mortality among younger patients (HR 10.89 [4.62–25.70], $P < 0.001$ for patients < 70 years and 2.78 [1.25–6.19], $P = 0.012$ among patients ≥ 70 years; $P = 0.023$ for the difference between the two subgroups) in the Munich cohort but not in the Tuebingen cohort (*Figure 4*). Although in the Tuebingen cohort there was a trend for better predictive power of DC_{st} among non-diabetics and patients with eGFR ≥ 60 mL/min/1.73 m^2, this did not reach statistical significance (*Figure 4*). Moreover, $DC_{st} \leq 2.5$ ms was a strong predictor of mortality in both acute and chronic MI [HR 5.36 (2.27–12.65), $P < 0.001$ for acute MI vs. 4.06, (1.75–9.40), $P = 0.001$ for chronic MI; $P = 0.211$ for the difference between the two subgroups].

Discussion

In the present study, we assessed DC from short-term ECG recordings under standardized conditions and tested its predictive value in two large cohorts of post-MI patients. Our findings demonstrate that DC_{st} is a strong predictor of 3-year mortality, which is independent from and incremental to that of established risk markers. The findings of our study therefore indicate that DC_{st} is a useful tool for bedside risk stratification that complements LVEF and clinical factors.

Heart rate variability refers to the variation over time of consecutive heart beat intervals and predominantly reflects the overall state of the autonomic nervous system. Heart rate variability has been conventionally analysed by means of time- and frequency- domain methods, as well as non-linear methods such as fractal scaling exponents.

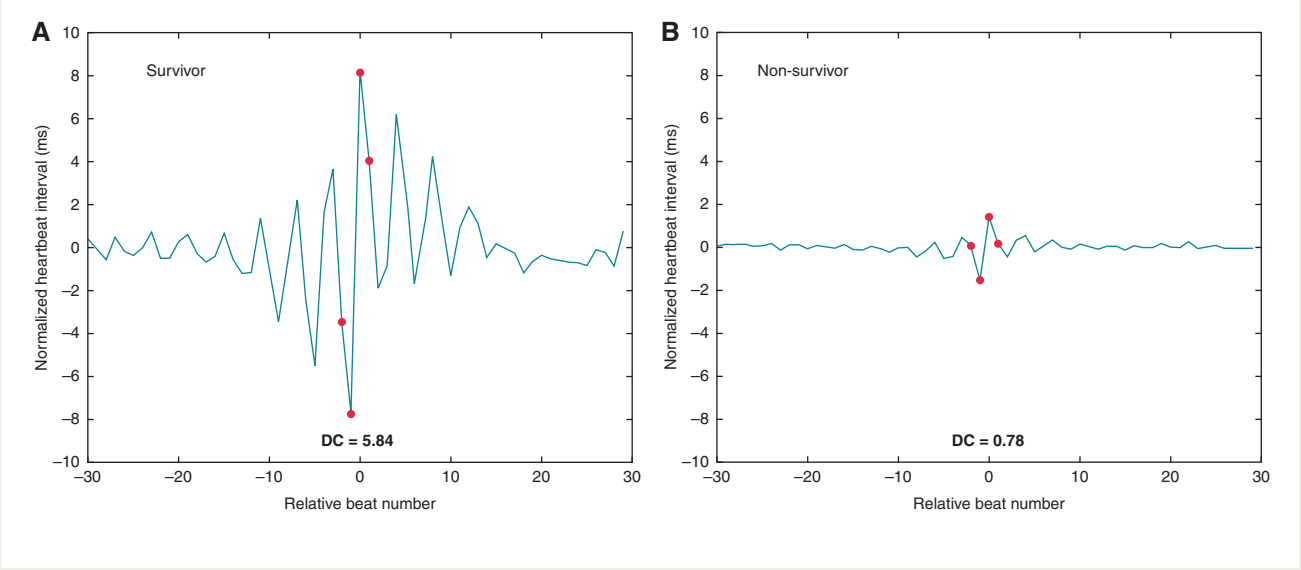

Figure 2 Typical phase-rectified signals from (*A*) a 57-year-old post-MI woman who survived the 3-year follow-up period and (*B*) a 48-year-old man who suddenly died 9 weeks after the index MI. In the surviving patient the amplitude of the phase-rectified signal is significantly higher compared to the non-surviving patient.

Table 2 Statistical association of clinical and HRV-markers with 3-year mortality in the Munich and Tuebingen cohorts

Characteristic	Munich cohort			Tuebingen cohort		
	Survivors	Non-survivors	*P*-value	Survivors	Non-survivors	*P*-value
Number of patients, *n*	860	48		430	48	
Age, years (IQR)	60 (17)	70 (9)	<0.001	65 (18)	72 (7)	<0.001
Females, *n* (%)	164 (19.1)	10 (20.1)	0.910	98 (22.8)	11 (22.9)	0.999
Acute MI, *n* (%)	860 (100)	48 (100)	n/a	209 (48.6)	23 (47.9)	0.999
Diabetes mellitus, *n* (%)	156 (18.1)	23 (47.9)	<0.001	184 (42.8)	26 (54.2)	0.176
Median LVEF, % (IQR)	53 (16)	44 (23)	<0.001	50 (15)	40 (20)	<0.001
GRACE, Score (IQR)	109 (32)	132 (24)	<0.001	132 (42)	163 (46)	<0.001
MHR, bpm (IQR)	62 (13)	69 (19)	0.033	65 (15)	70 (18)	0.003
DC_{24h}, ms (IQR)	5.3 (3.4)	2.8 (2.1)	<0.001	n/a	n/a	n/a
DC_{st}, ms (IQR)	4.8 (3.9)	2.0 (3.6)	<0.001	4.1 (4.0)	1.4 (3.5)	<0.001

DC_{st}, deceleration capacity assessed from short-term recordings; DC_{24h}, deceleration capacity assessed from 24-h Holter electrocardiograms; HRV, heart rate variability; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; LVEF, left-ventricular ejection fraction; MHR, mean heart rate from short-term recordings; MI, myocardial infarction n/a, not available.

Reduced HRV has been proven to be a strong and independent predictor of adverse outcome in the general population[10] and in patients with heart disease. The strong prognostic value of reduced HRV in post-MI patients has been documented in many studies. The multicenter post-infarction project (MPIP) showed that reduced HRV quantified by means of 24-h standard deviation of normal-to-normal RR intervals (SDNN) was a strong and independent predictor of 4-year mortality after acute MI.[11] These results have been validated in several prospective cohorts.[12,13] Other studies, including a reanalysis of MPIP have shown that reduced spectral measures of HRV in the very low- and low-frequency domain are also associated with increased risk of death.[14] More recently some new indices describing non-linear heart rate dynamics, such as fractal scaling exponents[15] and DC^5 of heart rate have been emerged. These markers are more robust to non-stationarities and artifacts and have been proven to yield stronger prognostic information than the traditional measures of HRV among post-MI patients. Heart rate turbulence is a method that in comparison to other HRV measures quantifies the physiological short-term oscillation of cardiac cycle length that follows spontaneous ventricular premature complexes. Heart rate turbulence alone[16] and in combination with other HRV parameters, such as DC^3 has been shown to be a strong predictor of mortality and SCD after acute MI. Besides MI, the prognostic meaning of HRV has been evaluated in various other cardiovascular diseases, including patients with chronic

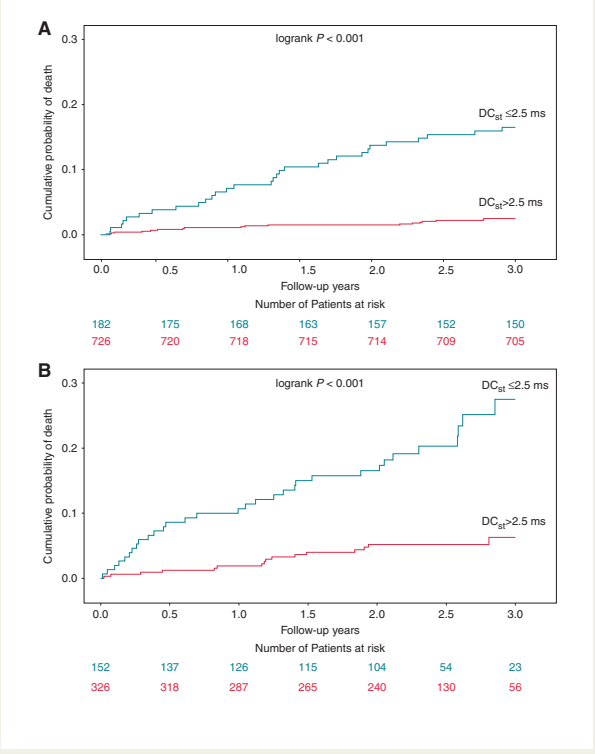

Figure 3 Cumulative 3-year mortality rates in patients stratified by $DC_{st} \leq 2.5$ ms in the Munich (*A*) and Tuebingen (*B*) cohorts, respectively.

heart failure,[17] patients with severe aortic stenosis[18] and patients presenting to the emergency department.[19]

One major problem of current autonomic risk markers is that their assessment is either too complicated or too time-consuming. In most clinical studies HRV was assessed from 24-h Holter recordings. Only very few studies have analysed the predictive value of HRV measures assessed from short-term recordings. Fei *et al.*[12] evaluated the predictive power of both short- and long-term HRV in 700 post-MI patients. Although the statistical association with cardiac mortality could be demonstrated for both, short-term SDNN and long-term HRVI, the predictive power of short-term SDNN was significantly lower than that of the 24-h HRVI. One reason for the lower predictive value of standard short-term HRV might be that spectral measures of short-term HRV are more prone to artifacts and noise, leading to substantial variations of normal values.[20] Assessment of short-term HRV by means of DC provides significant advantages over standard measures. Due to its underlying signal processing algorithm, DC is more robust to artifacts, noise, and non-stationarities. In addition, DC specifically captures deceleration-related oscillations of heart rate,[5,19] irrespective of their frequency, which are more closely related to vagal modulations. In our study, predictive power of DC_{st} was superior to other short-term HRV measures, including other non-linear indices of heart rate dynamics.

We also compared DC assessed from short-term and 24-h recordings. The two measurements were significantly correlated and their predictive value as estimated by ROC analysis was comparable. In multivariable analysis including both DC_{st} and DC_{24h}, DC_{st} was a significant and independent predictor of 3-year mortality, whereas DC_{24h} was not. One reason for the higher predictive value of DC_{st} in

Table 3 Univariable and multivariable cox regression analyses of the association of risk variables with 3-year total and cardiovascular mortality in the Munich and Tuebingen cohorts

Munich cohort				
All-cause mortality				
Risk variable	**Univariable cox regression**		**Multivariable cox regression**	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
GRACE score > 140	4.35 (2.36–8.01)	<0.001	1.91 (0.98–3.73)	0.059
LVEF ≤ 35%	5.27 (2.89–9.61)	<0.001	2.75 (1.43–5.27)	0.002
$DC_{st} \leq 2.5$ ms	7.18 (4.00–12.87)	<0.001	5.04 (2.68–9.49)	<0.001
Cardiovascular mortality				
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
GRACE score > 140	4.00 (1.75–9.14)	0.001	1.72 (0.69–4.27)	0.245
LVEF ≤ 35%	6.13 (2.81–13.38)	<0.001	3.47 (1.48–8.12)	0.004
$DC_{st} \leq 2.5$ ms	6.21 (2.88–13.37)	<0.001	4.18 (1.81–9.68)	<0.001
Tuebingen cohort				
All-cause mortality				
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
GRACE score >140	3.48 (1.89–6.42)	<0.001	2.29 (1.20–4.37)	0.012
LVEF ≤ 35%	4.16 (2.35–7.37)	<0.001	2.07 (1.11–3.86)	0.023
$DC_{st} \leq 2.5$ ms	4.57 (2.51–8.33)	<0.001	3.19 (1.70–6.02)	<0.001
Cardiovascular mortality				
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
GRACE score > 140	3.79 (1.57–9.16)	0.003	2.49 (0.98–6.35)	0.056
LVEF ≤ 35%	4.44 (1.99–9.93)	<0.001	2.31 (0.95–5.60)	0.065
$DC_{st} \leq 2.5$ ms	3.79 (1.66–8.67)	0.002	2.51 (1.04–6.03)	0.040

DC_{st}, deceleration capacity assessed from short-term recordings; GRACE, Global Registry of Acute Coronary Events; LVEF, left-ventricular ejection fraction.

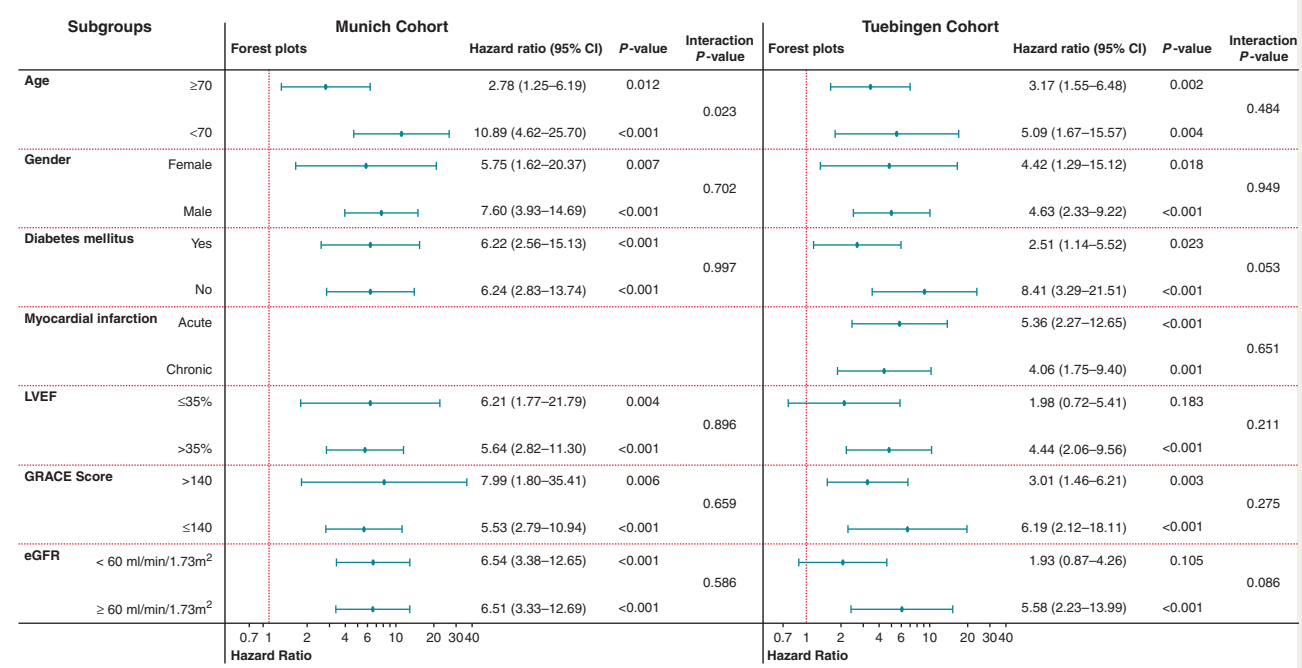

Figure 4 Hazard ratios of abnormal $DC_{st} \leq 2.5$ ms in different subgroups of patients in the Munich and Tuebingen cohorts. GRACE, Global Registry of Acute Coronary Events; eGFR, estimated glomerular filtration rate; LVEF, left-ventricular ejection fraction.

multivariable analysis might be that 30-min ECGs recordings are performed in standardized conditions compared to 24-h Holter recordings, which also include phases of physical activity, ECG lead displacement and non-stationarities created by variations in heart rate.

Clinical implications

An important finding of our study is that DC_{st} provides information of mortality risk on top of the information obtained by LVEF and GRACE score. In particular, in both Munich and Tuebingen cohorts the addition of DC_{st} led to a significant increase of C-statistics, IDI, and NRI scores. Assessment of DC from short-term recordings allows standardized, bedside risk assessment of post-MI patients, which makes the technology more suitable for clinical practice. Deceleration capacity-based risk assessment from short-term recordings could also open new perspectives in other fields of cardiac risk stratification, such as the integration of this technology in implantable devices.

Limitations

Our study has several limitations: first, autonomic function by means of DC can only be assessed in patients with sinus rhythm; second, in both cohorts, age was restricted to 80 years. The results cannot, therefore, be extrapolated to older patients; third, although we adjusted for various important risk predictors there are many other markers, such as heart rate recovery and brain natriuretic peptide, which were not routinely measured in this study; fourth, the use of total mortality as the primary endpoint has both advantages and disadvantages. Although the definition of death is without any ambiguity, the potential association with arrhythmic death might be lost. However, the incidence of unambiguous arrhythmic death in both cohorts was too low to power further statistical analyses.

Conclusion

In conclusion, DC_{st} is a strong and independent predictor of mortality and cardiovascular mortality after MI. The prognostic value of short-term DC is incremental to that of established risk markers, including LVEF and GRACE Score.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

The study was supported in part by grants from the program 'Angewandte klinische Forschung' (AKF) of the University of Tübingen 252-1-0 to A. Bauer. No additional external funding was received for this study. The Autonomic Regulation Trial (training cohort) was supported by Bundesministerium für Bildung, Wissenschaft, Forschung, und Technologie (13N/7073/7), the Kommission für Klinische Forschung and the Deutsche Forschungsgemeinschaft (SFB 386).

Conflict of interest: none declared.

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Autonomic Nervous System Activity as Risk Predictor in the Medical Emergency Department: A Prospective Cohort Study

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Objectives: To evaluate heart rate deceleration capacity, an electrocardiogram-based marker of autonomic nervous system activity, as risk predictor in a medical emergency department and to test its incremental predictive value to the modified early warning score.

Design: Prospective cohort study.

Setting: Medical emergency department of a large university hospital.

Patients: Five thousand seven hundred thirty consecutive patients of either sex in sinus rhythm, who were admitted to the medical emergency department of the University of Tübingen, Germany, between November 2010 and March 2012.

Interventions: None.

Measurements and Main Results: Deceleration capacity of heart rate was calculated within the first minutes after emergency department admission. The modified early warning score was assessed from respiratory rate, heart rate, systolic blood pressure, body temperature, and level of consciousness as previously described. Primary endpoint was intrahospital mortality; secondary endpoints included transfer to the ICU as well as 30-day and 180-day mortality. One hundred forty-two patients (2.5%) reached the primary endpoint. Deceleration capacity was highly significantly lower in nonsurvivors than survivors (2.9 ± 2.1 ms vs 5.6 ± 2.9 ms; $p < 0.001$) and yielded an area under the receiver-operator characteristic curve of 0.780 (95% CI, 0.745–0.813). The modified early warning score model yielded an area under the receiver-operator characteristic curve of 0.706 (0.667–0.750). Implementing deceleration capacity into the modified early warning score model led to a highly significant increase of the area under the receiver-operator characteristic curve to 0.804 (0.770–0.835; $p < 0.001$ for difference). Deceleration capacity was also a highly significant predictor of 30-day and 180-day mortality as well as transfer to the ICU.

Conclusions: Deceleration capacity is a strong and independent predictor of short-term mortality among patients admitted to a medical emergency department. (*Crit Care Med* 2015; 43:1079–1086)

Key Words: cardiac autonomic function; electrocardiogram; emergency department; heart rate variability; risk stratification

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Trial Registration: ClinicalTrials.gov NCT01486589.

Drs. Eick and Bauer developed the technology. Dr. Rizas did the statistical analyses. Drs. Eick, Rizas, and Bauer designed the study. Drs. Zürn and Groga-Bada organized the follow-up of the patients. Dr. Hamm critically revised the study. Drs. Kreth, Overkamp, and Weyrich were involved in patient enrollment. Dr. Gawaz helped to design the study. Dr. Bauer wrote the report with input from all other authors.

Dr. Bauer received a grant from the program "Angewandte klinische Forschung" of the University of Tübingen (252-1-0) and from the "Deutsche Stiftung für Herzforschung" (F/13/12). Dr. Bauer served as a board member for the Union Chimique Belge (UCB) advisory board; consulted for UCB; lectured for Medtronic; and received support for travel from Medtronic, Bayer, St Jude, and Guidant. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000000922

In most healthcare systems around the world, emergency departments (EDs) are the frontline venue to provide acute medical treatment. However, deficits in ambulatory care, demographic changes, and the rising complexity of diseases led to a dramatic increase in the number of admissions over the past years (1, 2). So-called ED overcrowding became a serious healthcare problem directly affecting the quality of patient care and mortality (3, 4). A recent population-based study showed an increase of intrahospital mortality by 79% when waiting times exceeded 6 hours (5).

Rapid risk stratification at first contact to define appropriate treatment priorities is of key importance to overcome limited resources. Current concepts of initial risk stratification are

based on clinical judgment, vital signs, including respiratory rate, heart rate, arterial blood pressure (BP), and body temperature, and neurological status. For clinical practice, these variables can be combined using a multivariable scoring system such as the "modified early warning score" (MEWS) (6–8). The MEWS can be quickly assessed within minutes by nursing staff before completion of any laboratory or other diagnostic tests. However, although the MEWS has been shown to significantly predict adverse events, it lacks both sensitivity and specificity for clinical decision making. Therefore, complementary approaches for risk stratification at first contact are of great clinical interest.

Essential information about the current condition of a patient can be derived from the functional status of the autonomic nervous system (ANS). The ANS is an integrated neural network connecting all vital organ systems. Severe damage of any organ within the network leads to a global change in the functional status of the ANS. Analyzing autonomic modulations of the sinus node by means of heart rate variability (HRV) has practical appeal as beat-to-beat intervals can be obtained noninvasively by a routine electrocardiogram (ECG) (9). Over the last decades, numerous measures have been proposed to assess HRV including standard measures in time and frequency domains (9) as well as complexity measures such as sample entropy (SampEN) or the multiscale sample entropy (MSE) index (10–13). Previous studies indicated that a depressed HRV has prognostic implications in various diseases, including myocardial infarction (14), heart failure (15), sepsis (16, 17), pulmonary diseases (18), stroke (19), hemorrhagic shock (20), renal failure (21), and trauma patients (22).

However, automated and reliable assessment of HRV in the setting of an ED is limited by the huge amount of noise and nonstationarities in ECG signals obtained under routine clinical conditions. Phase-rectified signal averaging (PRSA) is a robust signal processing algorithm that is capable of extracting periodic components out of noisy ECG signals. In previous studies, PRSA-based deceleration capacity (DC) of heart rate has been shown to yield strong and independent prognostic information in survivors of acute myocardial infarction (23, 24). DC is an integral measure of all deceleration-related oscillations of heart rate and considered to be a measure of overall tonic autonomic activity. Recently, we presented a refinement of the technology, including optimized R-peak detection and filtering techniques, allowing for a fully automated assessment of DC from unprocessed noisy ECG signals (25).

In the present study, we tested the prognostic power of DC in prediction of intrahospital mortality among patients admitted to a medical ED and compared it to standard and complexity measures of HRV. Furthermore, we aimed to assess the incremental value of DC to the MEWS model. We hypothesized that impaired DC was a strong and independent predictor of intrahospital mortality and that implementing DC into the MEWS model improved the predictive power of the MEWS model alone.

MATERIALS AND METHODS

Participants

Consecutive patients of either sex were prospectively enrolled between November 2010 and December 2012 if they were admitted to the medical ED of the University of Tübingen, Germany. Patients were included if they were 18 years old or older and presented in sinus rhythm, which is required for the assessment of cardiac autonomic function. **Figure 1** shows the flowchart of the validation cohort. The study was approved by the local ethics committee.

Biosignal Recording

The ED was equipped with six monitoring devices (DASH 4000/5000 and Teleguard, General Electrics, Fairfield, CT; sample frequency, 100 Hz). Nursing staff were advised to monitor patients directly after admission. Treating physicians were blinded to the study design. Management of patients in the ED was not influenced by monitoring. In particular, monitoring did not delay any diagnostic or therapeutic procedures.

Assessment of DC

Technical details of the methodology of automated assessment of DC have been described elsewhere (25). To account for the substantial noise and artifacts in the absence of manual editing, extensive filtering techniques and transformations were applied to the ECG raw signals to obtain the sequence of RR intervals. Briefly, a band-pass filter (4th order Chebyshev bandwidth filter 6–18 Hz) was applied to the signal followed by a 1st order forward differencing filter. Amplitudes were normalized and nonlinearly transformed using the Shannon energy envelope. Subsequently, a Hilbert

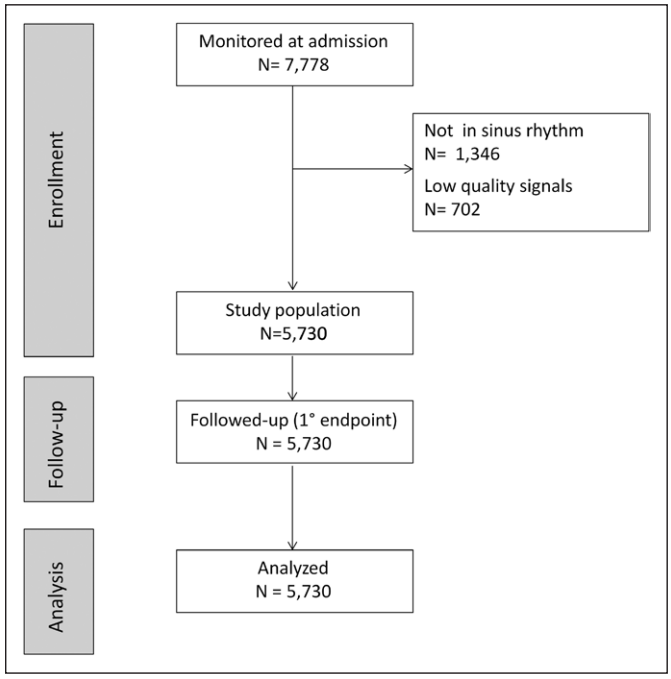

Figure 1. Enrollment, follow-up, and analysis of the study.

transformation and a moving average filter (250 samples) were applied followed by a Savitzky-Golay filter (frame 15, degree 0). Times of zero-crossing were identified and the R-peaks were searched.

The first 10 minutes of the recordings were used for DC computation. In case of low signal quality, the time frame was gradually extended to a maximum of 30 minutes until at least 200 anchors suitable for DC computation (see below) were detected. This led to an average recording time of 14.3 ± 8.5 minutes.

The RR time series were checked for the presence of atrial fibrillation using a validated automated algorithm (26). Recordings with atrial fibrillation were excluded from further analysis. The RR time series were transformed by PRSA (27) to obtain a modified, more robust version of DC (23). DC is an integral measure of the periodic power of all deceleration-related oscillations of heart rate in the observation period. The exact methodologies of PRSA and DC assessment have been described elsewhere (27). Briefly, instances within the RR interval time series are identified where the heart rate decelerates (so-called anchors). The central part of the PRSA signal is then quantified by Haar wavelet analysis to obtain an estimate of DC. The PRSA technology allows for several adjustments, which make the method more robust to artifacts and noise and improve agreement between automatically and manually processed ECGs (25). Here, we used $T = 4$ (instead of 1; equation 2a in [27]) and $s = 5$ (instead of 2; equation 8 in [27]). **Figure 2** exemplarily shows the phase-rectified signal of a patient who survived the hospital stay (**Fig. 2*A***) and the phase-rectified signal of a patient who died within the hospital stay (**Fig. 2*B***). In the nonsurviving patient (Fig. 2*B*), oscillations were blunted compared with the surviving patient (Fig. 2*A*).

In line with previous studies, patients were stratified according to DC to following risk categories: DC category 0 = low risk (> 4.5 ms); DC category 1 = intermediate risk (2.5–4.5 ms); and DC category 2 = high risk (≤ 2.5 ms) (23).

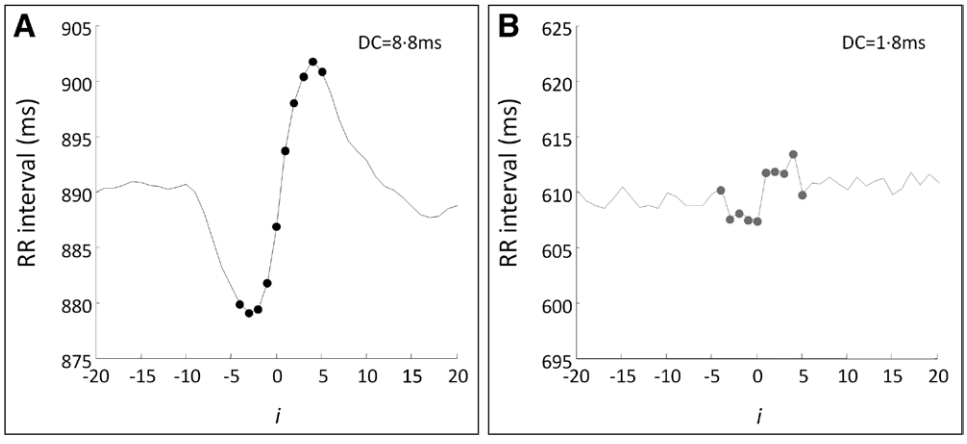

Figure 2. Representative phase-rectified signals from 10-min recordings of heartbeat intervals in one patient who survived the hospital stay (**A**) and one patient who died during the hospital stay (**B**). In the surviving patient, the amplitude of the phase-rectified signal is significantly greater compared with the nonsurviving patient. Bolded points = values of phase-rectified signal used for computation of deceleration capacity (DC), *i* = index of phase-rectified signal *X(i)*.

Assessment of Standard and Complexity Measures of HRV

For assessment of standard and complexity measures of HRV, the first 30 minutes of the recordings were analyzed. In cases of lower recording time, the total length of the recording was used. Measures of HRV were calculated for segments of 256 RR intervals and subsequently averaged. Segments with excessive artifact burden (> 50%) were disregarded. We assessed following standard measures of HRV in the time and frequency domain in line with recommendations of the task force (9): the standard deviation of all normal-to-normal intervals (SDNNs), the HRV index, the root mean square of the successive difference, the power in the low frequency (LF; 0.04–0.15 Hz) and high frequency (HF) ranges (0.15–0.4 Hz), and the ratio between LF and HF. We also assessed two complexity measures of HRV, SampEn and the MSE index. For calculation of SampEn, we used $m = 2$ and $r = 6$ ms in line with previous reports (12). MSE index was defined as the summation of the SampEn values for scales 1–4 (12).

Assessment of the MEWS

The MEWS was calculated from physiological variables, including respiratory rate, heart rate, systolic BP, and body temperature and level of consciousness at ED admission, as previously described (7). The MEWS can range from 0 (lowest risk) to 14 (highest risk).

Study Endpoints

The primary endpoint was intrahospital mortality. Secondary endpoints were total mortality at 30 and 180 days as well transfer to the ICU during the hospital stay.

Follow-Up

Intrahospital deaths were monitored via the electronic hospital information system. Patients were followed up at intervals of 30 and 180 days after admission to the ED. Information about the patient's status after ED discharge was also derived from the hospital information system in patients who were readmitted to the hospital. The status at 30 days after admission to the ED was available in all patients. The status at 180 days after admission to the ED was available in 97.5% of the patients. Patients who were lost to follow-up were censored at the date of latest contact.

Statistical Analyses

Continuous variables are presented as the mean and SD and were compared using the Mann-Whitney *U* test. Qualitative data are expressed

as percentages and were analyzed using the chi-square test. Receiver-operator characteristic (ROC) curves were constructed for all tested predictors by plotting 1 – specificity versus sensitivity. ROC curves were quantified by the area under the curve (AUC). To test the difference between ROC curves, we used bootstrapping based on the creation of pseudo-replicate datasets by random resampling of the dataset *n* times for error estimation ($n = 1{,}000$ in this study) (28). The association of risk variables with the primary endpoint was tested by univariable and multivariable logistic regression analyses. Multivariable analyses were adjusted for age and gender. In logistic regression analyses, coefficients were standardized by the procedure suggested by Menrad (29). To test the incremental prognostic value of DC on top of the MEWS model, we implemented *C*-statistic and integrated discrimination improvement (IDI) score (30). Mortality rates were estimated by the Kaplan-Meier method (31). Odds ratios are presented with 95% CIs. Differences were considered statistically significant when *p* value is less than 0.05. Statistical analyses were performed using CRAN R 2.15.2 and SPSS 20.0 (SPSS: IBM, Armonk, NY).

Sample Size Calculation

The sample size was defined by the number of endpoints with a maximum of 10,000 patients to be screened. Based on previous work, we postulated that 10 endpoints per risk predictor should be on hand (32). We aimed to include a sample size with at least 100 patients reaching the primary endpoint, which allows for multivariable analysis with more than 10 variables to be included.

RESULTS

Table 1 shows the patients' characteristics. Main causes for admission to the ED were cardiovascular and gastrointestinal diseases followed by oncologic, hematologic, and pulmonary diseases. During the hospital stay, 142 patients died (2.5%). After 30 and 180 days, these figures were 196 (3.4%) and 436 patients (7.6%), respectively. As shown in **Table 2**, nonsurviving patients were older and had higher heart rates and respiratory rates but lower systolic, mean, and diastolic arterial blood pressures and low levels of consciousness. Correspondingly, the MEWS score was substantially higher in nonsurviving than surviving patients (3.5 ± 1.7 vs 2.3 ± 1.4; $p < 0.001$).

Table 3 shows the statistical association of markers of HRV with intrahospital mortality. DC was significantly lower in nonsurvivors than survivors (2.9 ± 2.1 ms vs 5.6 ± 2.9 ms; $p < 0.001$). Also standard and complexity measures of HRV were highly significantly associated with the primary endpoint. Nonsurviving patients had lower levels of time and frequency domain measures of HRV ($p < 0.001$ for all) as well as lower levels of SampEn and MSE-index ($p < 0.001$ for both). Table 3 also shows the areas under the ROC curves for prediction of intrahospital mortality. Among all HRV measures tested, DC yielded the greatest area under the curve followed by the HRV index and the MSE index.

TABLE 1. Patients' Characteristics and Outcomes of the Study Population

No. of patients	5,730
Age	61.2 ± 17.7
Female (%)	2,605 (45.5)
Main causes for emergency department admission, *n* (%)	
Cardiovascular	3,427 (59.8)
Gastrointestinal	565 (9.9)
Oncological and hematologic	214 (3.7)
Pulmonary	412 (7.2)
Endocrinologic	128 (2.2)
Infectiologic	178 (3.1)
Renal	49 (0.9)
Other	757 (13.2)
Admission to ICU (%)	366 (6.4)
Duration of hospital stay (d)	6.1 ± 8.9
Intrahospital deaths (%)	142 (2.5)
Deaths at 30 days (%)	196 (3.4)
Deaths at 180 days (%)	436 (7.6)

Table 4 shows the univariable and multivariable logistic regression analyses for prediction of intrahospital mortality. On univariable analysis, the MEWS and all measures of HRV were significantly associated with intrahospital mortality. On multivariable analysis, however, only the MEWS and DC provided independent prognostic information (standardized coefficients of 1.14 and 0.85, respectively; $p < 0.001$ for both). All other markers of HRV were not independently associated with intrahospital mortality.

Figure 3 shows the ROC curve analyses for prediction of intrahospital mortality by DC, the MEWS, and the combination of DC and the MEWS. DC yielded an AUC of 0.780 (95% CI, 0.745–0.813; $p < 0.001$) (**Fig. 3*A***). The MEWS model yielded an AUC of 0.706 (0.667–0.750; $p < 0.001$) (**Fig. 3*B***). Implementing DC into the MEWS model led to a highly significant increase of the AUC to 0.804 (0.770–0.835; $p < 0.001$ for difference) (Fig. 3*B*). The relative IDI was 60% ($p < 0.001$).

Using the established risk categories, DC classified 3,595 (62.7%), 1,157 (20.2%), and 901 (15.7%) patients as low-risk (DC category 0), intermediate-risk (DC category 1), and high-risk patients (DC category 2), respectively. Of these, 26 (0.7%), 39 (3.4%), and 77 patients (7.9%) died during the hospital stay ($p < 0.001$). We also assessed whether DC was a predictor of long-term mortality. **Figure 4** shows cumulative 180-day mortality rates of patients stratified by DC categories. At 30 days, cumulative mortality rates were 0.9%, 5.5%, and 10.1% in the low-, intermediate-, and high-risk groups, respectively ($p < 0.001$). At 180 days, these figures were 2.7%, 12.0%, and 21.0%, respectively ($p < 0.001$).

TABLE 2. Statistical Association of Clinical and Physiological Markers With Intrahospital Mortality

Variable	Survivors	Nonsurvivors	*p*
Demographics			
Patient age (yr)	60.9 ± 17.8	70.5 ± 12.9	< 0.001
Female, %	45.5	43.0	0.386
Physiologic markers			
Heart rate (beats/min)	83.5 ± 24.9	95.6 ± 23.7	< 0.001
Mean blood pressure (mm Hg)	96 ± 18	84 ± 18	< 0.001
Systolic blood pressure (mm Hg)	144 ± 26	125 ± 28	< 0.001
Diastolic blood pressure (mm Hg)	79 ± 19	68 ± 15	< 0.001
Respiratory rate (breaths/min)	16.5 ± 1.8	17.5 ± 1.9	< 0.001
Body temperature (°C)	36.2 ± 0.7	36.2 ± 0.8	0.783
Level of consciousness (according to the alert, voice, pain, unresponsive scale) (%)			
Alert	5,454 (97.6)	135 (95.1)	< 0.001
Reaction to voice	37 (0.6)	6 (4.2)	
Reaction to pain	96 (1.7)	1 (0.7)	
Unresponsive	1 (< 0.1)	0 (0)	
Modified early warning score (score points)	2.3 ± 1.4	3.5 ± 1.7	< 0.001

Cause of admission had no significant influence on the predictive value of DC. DC was a significant predictor of mortality in the 3,427 patients admitted for cardiovascular causes (AUC, 0.767 [0.707–0.827]; $p < 0.001$) as well as in the 2,303 patients admitted for noncardiovascular causes (AUC, 0.768 [0.725–0.811]; $p < 0.001$). Furthermore, DC was significantly lower in the 366 patients who were transferred to the ICU during their hospital stay than in patients who were not transferred (3.8 ± 2.7 ms vs 5.7 ± 2.9 ms; $p < 0.001$).

DISCUSSION

The main findings of our study indicate that DC is a strong predictor of intrahospital mortality in patients admitted to a medical ED. Its prognostic value was independent of established measures of HRV and significantly improved the MEWS model, which is an established scoring system for early risk stratification in the ED. The predictive power of DC was comparable for patients admitted for cardiovascular and noncardiovascular diseases. DC was also a strong predictor of 30-day and 180-day mortality.

Previous studies have shown that reduced HRV is associated with poor outcome in various cardiac and noncardiac diseases (14–16, 18–21). However, only very few studies tested the clinical usefulness of HRV as clinical tool for risk prediction in a medical ED (33). DC differs from standard measures of HRV in several aspects. First, due to its underlying signal processing algorithm, DC is robust to artifacts, noise, and nonstationarities. This is of particular advantage when analyzing biological signals that are recorded under uncontrolled conditions in the setting of an ED (25). Second, DC is an integral measure of all deceleration-related periodic components of HRV, irrespective of their frequency. Thus, DC is not driven by any specific physiological mechanism but rather influenced by alterations of the vagal, sympathetic, vascular, and humoral systems. Thereby, DC differs from traditional spectral measures of HRV, which assess the spectral power in distinct frequency bands. Global measures of HRV, such as SDNN or HRV index, also include nonperiodic patterns of HRV, which might not be directly related to autonomic mechanisms.

In contrast to previous studies (23), DC was assessed from short-term ECG recordings, which raises both methodological and physiological questions. First, the number of segments entering the PRSA-averaging process is much smaller compared to a full 24-hour Holter recording that might limit the capability of eliminating noise and artifacts. Second, short-term DC does not reflect ultra and very low-frequency oscillations. DC as assessed in the present study should therefore be interpreted as measure of short-term cardiovascular control.

In our study, the prognostic performance of DC was statistically superior to that of other measures of HRV. However, it needs to be emphasized that direct comparisons between DC and other metrics might be difficult. Several requirements for assessment of traditional measures of HRV, particularly in the frequency domain, were not met, including stationarity of the signal and manual preprocessing of the raw data (9). Notably, the complexity measures SampEN and MSE index that quantify the amount predictability of the signal were strong predictors of mortality in our population. As previous studies have

TABLE 3. Statistical Association of Markers of Heart Rate Variability With Intrahospital Mortality

Variable	Survivors	Nonsurvivors	*p*	Area Under the Receiver-Operator Characteristic Curve (95% CI)	*p*
Deceleration capacity	5.6 ± 2.9	2.9 ± 2.1	< 0.001	0.780 (0.745–0.813)	< 0.001
Standard deviation of all normal to-normal intervals	42.7 ± 29.6	29.3 ± 21.4	< 0.001	0.658 (0.608–0.708)	< 0.001
Root mean square of successive differences of all normal-to-normal intervals	22.6 ± 12.6	19.8 ± 12.3	< 0.001	0.598 (0.542–0.654)	< 0.001
Heart rate variability triangular index	6.0 ± 2.9	3.8 ± 2.3	< 0.001	0.744 (0.699–0.789)	< 0.001
LF	614.1 ± 1229.3	348.8 ± 783.3	< 0.001	0.662 (0.611–0.712)	< 0.001
HF	187.0 ± 270.5	128.0 ± 182.0	< 0.001	0.602 (0.548–0.656)	< 0.001
LF/HF	3.8 ± 4.2	2.5 ± 3.2	< 0.001	0.654 (0.606–0.701)	< 0.001
Sample entropy	1.8 ± 0.5	1.4 ± 0.5	< 0.001	0.677 (0.625–0.729)	< 0.001
Multiscale entropy index	5.0 ± 2.1	3.2 ± 2.0	< 0.001	0.736 (0.689–0.783)	< 0.001

LF = power in the low-frequency range, HF = power in the high-frequency range.

shown that SampEN and MSE index are highly sensitive to their respective input variables *m*, *r*, and scale (12), future studies are needed to test whether the prognostic ability of these complexity measures might be optimized by refined settings.

We assessed the predictive value of DC and the MEWS model by ROC curve analysis, which is independent from selection of specific cutoff values. The largest separation of ROC curves between DC and the MEWS model occurred at high sensitivity levels of 80%. At this level of sensitivity, the corresponding specificity of DC was substantially higher than that of the MEWS model. Hence, DC-based risk assessment is particularly useful for a better identification

TABLE 4. Univariable and Multivariable Binary Logistic Regression Analysis for Prediction of Intrahospital Mortality

	Univariable Analysis			Multivariable Analysis		
Variable	OR (95% CI)	*z*	*p*	OR (95% CI)	*z*	*p*
Modified early warning score	1.28 (1.22–1.35)	9.7	< 0.001	1.14 (1.09–1.19)	5.8	< 0.001
deceleration capacity	0.75 (0.71–0.79)	10.0	< 0.001	0.81 (0.74–0.89)	4.3	< 0.001
Standard deviation of all normal to-normal intervals	0.83 (0.79–0.89)	5.5	< 0.001	1.01 (0.92–1.11)	0.2	0.835
Root mean square of successive differences of all normal-to-normal intervals	0.93 (0.87–0.98)	2.5	0.012	1.05 (0.97–1.13)	1.2	0.213
Heart rate variability triangular index	0.76 (0.72–0.81)	8.3	< 0.001	0.91 (0.75–1.11)	0.9	0.358
LF	0.90 (0.84–0.97)	2.9	0.003	1.01 (0.92–1.10)	0.2	0.879
HF	0.92 (0.86.0.98)	2.5	0.011	0.98 (0.90–1.07)	0.4	0.687
LF/HF	0.88 (0.82–0.94)	3.9	< 0.001	0.99 (0.93–1.07)	0.1	0.886
Sample entropy	0.83 (0.78–0.88)	6.3	< 0.001	0.99 (0.89–1.09)	0.3	0.778
Multiscale entropy index	0.77 (0.72–0.82)	8.6	< 0.001	1.01 (0.83–1.23)	0.1	0.913

OR = odds ratio, LF = power in the low-frequency range, HF = power in the high-frequency range.
Multivariable analysis adjusted for age and gender; standardized coefficients presented.

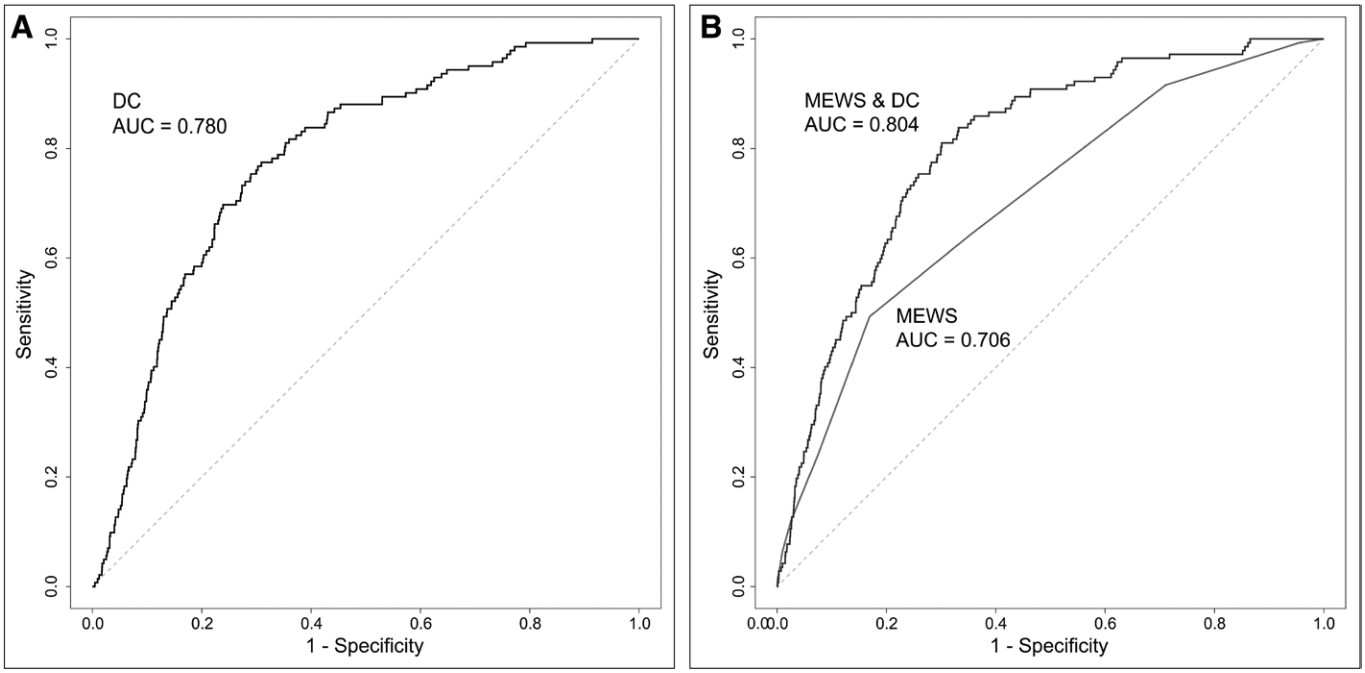

Figure 3. Receiver-operator characteristic curves for prediction of intrahospital mortality. **A**, Deceleration capacity (DC). **B**, The modified early warning score (MEWS) as well as the combination of the MEWS and DC. The difference between the area under the receiver-operator characteristic curve (AUC) of the MEWS and the combination of the MEWS and DC was highly significant ($p < 0.001$).

of low-risk patients who could be treated with less priority. This was also confirmed when using DC risk categories. DC greater than 4.5 ms classified almost two thirds of patients as low-risk patients. These patients were at very low risk of death (0.7%; 26 deaths in 3,595 patients). By contrast, DC less than or equal to 2.5 ms identified a smaller high-risk group of 978 patients (17% of admitted patients) who were at an almost 12-fold risk of death compared with the low-risk group. Our findings therefore suggest that these patients should be treated with high priority. In this context of note, impaired DC at admission also predicted later transfer to the ICU. Extended follow-up to 6 months revealed that impaired DC was also a strong predictor of late mortality. Patients with DC less than or equal to 2.5 ms at admission had a cumulative 6-month mortality rate of 21%, indicating that these patients should be closely monitored after discharge. Importantly, risk predictive power of DC was equally strong in both cardiovascular and noncardiovascular patients. It needs to be mentioned that the used cutoff values have been derived from 24-hour Holter recordings in postinfarction patients. Post hoc analyses revealed an optimum cutoff value of 3.2 ms for DC in the study population, which needs to be validated in further studies.

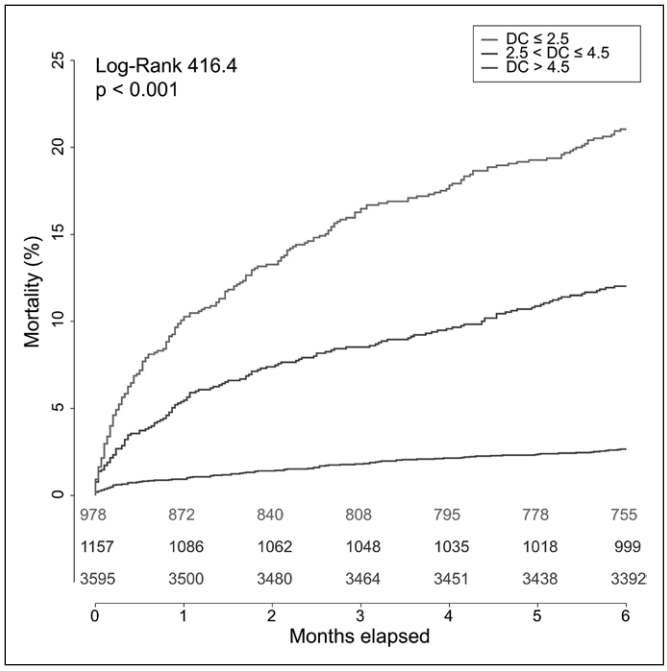

Figure 4. Cumulative 180-day mortality rates in patients stratified by deceleration capacity (DC) risk categories. The numbers of patients in the individual groups involved in the analysis at 0, 45, 90, 135, and 180 days are shown under the graph.

The limitations of our study need to be recognized. First, autonomic function by means of HRV can only be assessed in patients with sinus rhythm. Second, our study was performed in a medical ED. Further investigations are necessary to determine whether DC provides prognostic value in different settings. Furthermore, we did not compare the predictive value of DC to biochemical markers such as the sensitive troponins or C-reactive protein. We also cannot rule out that assessment of other markers might have influenced triage in our ED. Finally, as our study was purely observational, it needs to be shown whether clinical decision making based on DC and other predictors leads to a better outcome.

CONCLUSIONS

In conclusion, assessment of the ANS activity by DC provides strong and independent prognostic information in patients admitted to a medical ED. DC can be obtained fully automatically within minutes at first contact and significantly improves established risk stratification models. The technology is inexpensive, readily available, and can be implemented in existing monitoring devices. Further technical developments might realize the integration of the technology into cheaper mobile devices, which could be used in waiting halls of ED or in ambulatory settings.

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Clin Res Cardiol
DOI 10.1007/s00392-017-1104-3

ORIGINAL PAPER

Point-of-care testing of cardiac autonomic function for risk assessment in patients with suspected acute coronary syndromes

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Received: 28 September 2016 / Accepted: 8 March 2017

Abstract
Background Impaired cardiac autonomic function has been linked to adverse outcomes in patients with acute coronary syndromes (ACS) but is not included in clinical risk models. This is the first study to investigate whether point-of-care testing of cardiac autonomic function by means of short-term deceleration capacity (DC) of heart rate improves risk assessment in patients with suspected ACS.
Methods 1821 patients with suspected ACS were prospectively enrolled if they were older than 17 years and in sinus rhythm. Short-term DC was automatically assessed from monitor recordings at hospital admission. The Global Registry of Acute Coronary Events (GRACE) score was used as gold standard risk predictor. Primary endpoint was the composite of intrahospital and 30-day mortality. Secondary endpoint was 180-day mortality.
Results Of the 1,821 patients with suspected ACS, 28 (1.5%) and 60 (3.3%) reached the primary and secondary endpoints, respectively. DC was a highly significant predictor of both endpoints, yielding areas under the curve (AUC) of 0.784 (95% CI 0.714–0.854) and 0.781 (0.727–0.832) ($p<0.001$ for both), respectively. Implementing DC into the GRACE-risk model leads to a significant increase of the C-statistics from 0.788 (0.703–0.874) to 0.825 (0.750–0.900; $p<0.01$ for difference) and from 0.814 (0.759–0.864) to 0.851 (0.808–0.889; $p<0.01$ for difference) for the primary and secondary endpoints, respectively. Stratification by dichotomized DC was especially powerful in patients with GRACE score <140.
Conclusions In patients with suspected ACS, point-of-care testing of cardiac autonomic function by means of DC is feasible and improves risk assessment by the GRACE score.
Clinical Trial Registration Clinicaltrials.gov NCT01486589.

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Published online: 22 March 2017

Keywords Acute coronary syndrome · ECG · Autonomic nervous system · Risk stratification

Introduction

Patients with acute coronary syndrome (ACS) represent a highly heterogeneous population with respect to their risk for developing adverse events. Therefore, early risk stratification is essential to guide optimum tailored treatment. The Global Registry of Acute Coronary Events (GRACE) score is currently believed to provide the most accurate risk stratification in ACS patients [1, 2]. Although the strong prognostic value of the GRACE score has been validated by many studies [3–5], risk stratification particularly in low-risk patients with ACS still needs to be improved.

Experimental and clinical studies indicated that in cardiac patients, important prognostic information could be derived from the functional status of the cardiac autonomic nervous system [6–10]. In the setting of acute myocardial ischemia, impaired cardiac autonomic function has been linked to increased mortality risk [11]. Deceleration capacity (DC) of heart rate is an ECG-based risk marker that captures autonomic activity-related modulations of heart rate [9]. In post-infarction patients, decreased DC was shown to be a strong and independent predictor of late mortality that was superior to standard measures of heart rate variability and established risk predictors [7, 9]. We have developed a computer-based technology that allows automated point-of-care assessment of DC from short-term monitor recordings [12, 13].

In the present study, we, therefore, hypothesized that short-term DC yields important prognostic information in patients with suspected ACS and significantly improves risk prediction by the GRACE score.

Methods

The study included 1,821 consecutive patients who presented with symptoms suspected of ACS in the chest-pain unit of the university of Tuebingen, Germany, between November 2010 and December 2012. Patients were excluded if they were younger than 18 years or not in sinus rhythm (Fig. 1). The present study is a substudy of a larger study (*NCT01486589* [13]) which evaluated the predictive value of cardiac autonomic function for risk assessment in 5,730 all-comers to a large medical emergency university department. The present study was designed to assess the prognostic value of DC in patients with suspected acute coronary syndromes.

Nursing staff was advised to monitor patients directly after admission (DASH 4000/5000 and Teleguard, General

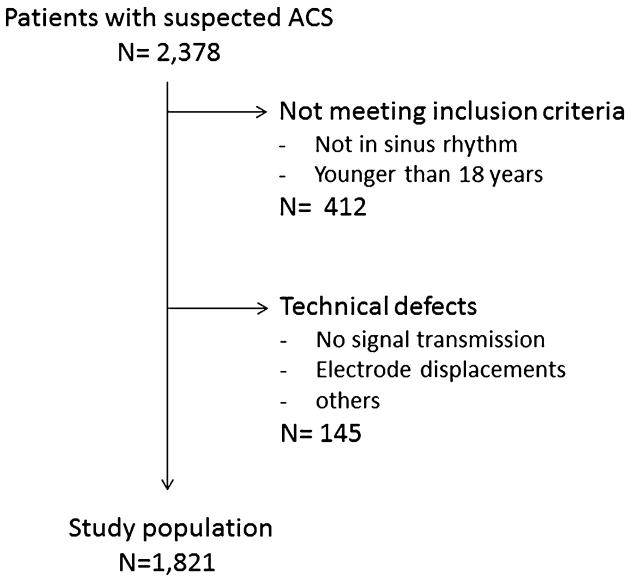

Fig. 1 Flow chart of the study population

Electrics, Fairfield, CT; sample frequency, 100 Hz). Treating physicians were blinded to the study design. Monitoring did not influence management of the patients. Assessment of DC was performed before any invasive treatment.

Technical details of automated assessment of DC have been described elsewhere [8, 9, 12]. To account for the substantial noise and artifacts in the absence of manual editing, extensive filtering techniques and transformations were applied to the ECG raw signals to obtain the sequence of RR intervals. Briefly, a band-pass filter (fourth-order Chebyshev bandwidth filter 6–18 Hz) was applied to the signal followed by a first-order forward differencing filter. Amplitudes were normalized and non-linearly transformed using the Shannon energy envelope. Subsequently, a Hilbert transformation and a moving average filter (250 samples) were applied followed by a Savitzky–Golay filter (frame 15, degree 0). Times of zero-crossing were identified, and the R-peaks were searched.

The first 10 min of the recordings were used for DC computation. In case of low signal quality, the time frame was gradually extended to a maximum of 30 min until at least 200 anchors suitable for DC computation were detected. The mean record times was 12.6 ± 5.0 min. The determination of DC can be computerized, within seconds.

The RR time series was checked for the presence of atrial fibrillation using a validated automated algorithm [14]. Recordings with atrial fibrillation were excluded from further analysis. The RR time series were transformed by phase-rectified signal averaging [15] to obtain a modified, more robust version of DC [9]. DC is an integral measure of the periodic power of all deceleration-related oscillations of heart rate in the observation period. The exact

methodologies of phase-rectified signal averaging and DC assessment have been described elsewhere [15]. Briefly, instances within the RR interval time series are identified, where the heart rate decelerates (so-called anchors). The central part of the phase-rectified signal averaging signal is then quantified by Haar wavelet analysis to obtain an estimate of DC. The phase-rectified signal averaging technology allows for several adjustments, which make the method more robust to artifacts and noise and improve agreement between automatically and manually processed ECGs [16]. Here, we used $T=4$ (instead of 1; Eq. 2a in [15]) and $s=5$ (instead of 2; Eq. 8 in [15]).

The GRACE score for prediction of the intrahospital mortality was calculated as previously described [2] and included following variables: age, systolic blood pressure, heart rate, Killip classification, creatinine, cardiac arrest at admission, ST-segment deviation, and cardiac biomarkers. In the present study, sensitive troponine I was used as cardiac biomarker.

Left ventricular ejection fraction was not routinely assessed at hospital admission.

The primary endpoint was the composite of intrahospital mortality and 30-day mortality. The secondary endpoint was 180-day mortality. Intrahospital deaths were monitored via the electronic hospital information system and classified by independent physicians who received pseudonymized patient data. To obtain information about outcome after hospital discharge, patients were contacted by phone call 180 days thereafter. 180-day follow-up information was available in all patients.

Continuous variables are presented as mean ± standard deviation and were compared using the Mann–Whitney *U* test. Qualitative data are expressed as percentages and were analyzed using the Chi-square test. Receiver–operator characteristic (ROC) curves were constructed for risk predictors by plotting 1—specificity vs. sensitivity. ROC curves were quantified by the area under the curve (AUC). To test the difference between ROC curves, bootstrapping was employed based on the creation of pseudo-replicate data sets by random resampling of the data set n times for error estimation ($n=1000$ in this study). The association of risk variables with the endpoints was tested by univariable and multivariable Cox-regression analyses. Multivariable analyses included DC as well as the single components of the GRACE score: age, systolic blood pressure, heart rate, Killip classification, creatinine, cardiac arrest at admission, ST-segment deviation, and cardiac biomarkers. To test the incremental prognostic value of DC on top of the GRACE-risk model, we implemented *C*-statistic and continuous net reclassification improvement (NRI). Mortality rates were estimated by the Kaplan–Meier method. Hazard ratios were presented with 95% CIs. When used as categorical variable, DC was dichotomized at the established cut-off values of 2.5 and 4.5 ms, respectively [9]. Two-tailed Fisher exact test was used to compare sensitivities (proportion between true positive and false negative) and positive predictive accuracies (proportion between true positive and false positive) in different selections of high-risk groups. Differences were considered statistically significant when p value was less than 0.05. Statistical analyses were performed using CRAN R 3.0.1 and SPSS 21.0 (SPSS: IBM, Armonk, NY).

Results

Table 1 shows the patients' characteristics. Mean age was 60.7 years, and 38% of the patients were female. 21.9% of the patients had elevated cardiac troponins, 10.1% of the patients showed ST-deviations on the ECG. 931 (51%) of the patients underwent invasive diagnostic testing, and out of whom 838 (90%) were treated by PCI. Of the 1,821 patients with suspected ACS, the final diagnosis of ACS was made in 910 patients (50.0%). Among them, 99 patients (5.4%) had ST-elevation myocardial infarction (STEMI), 312 (17.1%) had non-ST-elevation myocardial

Table 1 Patients' characteristics and outcomes of the study population

Variable	
Number of patients	1821
Age (years)	60.7 ± 16.3
Females	695 (38.2%)
History of previous MI	338 (18.6%)
Known congestive heart failure	252 (13.8%)
Cardiovascular risk factors	
Hypertension	1110 (61.0%)
Diabetes mellitus	340 (18.6%)
Hyperlipidemia	615 (33.8%)
Smoking	378 (20.8%)
Family history of CVD	359 (19.7%)
History of PCI	566 (31.1%)
Invasive diagnostic and treatment	
Coronary angiography	931 (51.0%)
PCI	838 (46.0%)
Diagnosis at hospital discharge	
STEMI	99 (5.4%)
NSTEMI	312 (17.1%)
Unstable angina pectoris	499 (27.4%)
Chest pain	911 (50.0%)
Outcomes	
Intrahospital and 30-day mortality	28 (1.5%)
180-day mortality	60 (3.3%)

CVD cardiovascular disease, *MI* myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-elevation myocardial infarction

infarction (NSTEMI), and 499 (27.4%) had unstable angina pectoris (UAP).

Twenty-eight patients (1.5%) died within 30 days after hospital admission. 60 patients (3.3%) died within 180 days after hospital admission. Table 2 shows patients' characteristics of patients reaching and not reaching the primary and secondary endpoints.

DC was substantially lower in patients reaching the primary and secondary endpoints than in those who did not (3.9 ± 2.0 vs. 6.6 ± 2.9 and 3.8 ± 2.5 vs. 6.7 ± 3.8 ms for the primary and secondary endpoints, respectively, $p < 0.001$ for both). Highly significant differences were also noted for the GRACE score (146.4 ± 47.0 vs. 99.7 ± 32.7 and 143.6 ± 39.7 vs. 98.9.5 ± 32.2 for the primary and secondary endpoints, respectively, $p < 0.001$ for both). DC yielded AUCs of 0.784 (95% CI 0.714–0.854) and 0.781 (0.727–0.832) for the primary and secondary endpoints, respectively ($p < 0.001$ for both) (Fig. 2a, c). The GRACE score yielded AUCs of 0.788 (0.703–0.874) and 0.814 (0.759–0.864), respectively (Fig. 2b, d).

Figure 3A shows cumulative mortality rates of patients stratified by DC. The 168 patients with DC ≤ 2.5 ms had the worst prognosis with a 180-day mortality rate of 12.5%, while the 1421 patients with DC > 4.5 ms had the best prognosis with a 180-day mortality rate of 1.8%. The 232 patients with DC 2.5–4.5 ms had an intermediate prognosis with a 180-day mortality rate of 6.0% ($p < 0.001$ for overall difference).

Tables 3 and 4 show uni- and multivariable analyses of DC and the single components of the GRACE score for prediction of both endpoints. DC was the second strongest risk predictor of the primary endpoint following cardiac arrest at hospital admission and was the strongest risk predictor of the secondary endpoint. Implementing DC into the GRACE-risk model led to a highly significant increase of the C-statistics of both endpoints to 0.825 (0.750–0.900; $p < 0.01$ for difference, continuous NRI 0.593, $p < 0.01$) and 0.851 (0.808–0.889; $p < 0.01$ for difference, continuous NRI 0.698, $p < 0.01$) for the primary and secondary endpoints, respectively (Fig. 2b, d).

1121 of the 1821 patients were on betablockers at hospital admission, while 700 patients were not. Betablocker treatment was strongly associated with the presence or absence of an acute coronary syndrome [OR 17.2 (13.4–22.2), $p < 0.001$]. DC was significantly lower in patients on betablockers than in patients off betablockers (6.2 ± 3.1 vs. 7.3 ± 2.3 ms; $p < 0.001$), most probably related to the different patients' characteristics. Adjusting the multivariable models by betablocker treatment did not affect the prognostic value of DC with respect to prediction of the primary or secondary endpoint.

We also tested the risk predictive power of DC for prediction of 180-day mortality in subgroups of patients with a GRACE score < 140 ($n = 1604$) and ≥ 140 ($n = 217$). As shown in Fig. 3b and c, risk stratification by DC was highly significant in the 1604 patients with a GRACE score < 140 ($p < 0.001$), while in the 217 patients with a GRACE score ≥ 140, there was no significant separation ($p = 0.178$). Among the 1,604 patients with a GRACE score < 140, DC ≤ 2.5 ms identified 111 high-risk patients with a 180-day mortality of 9.0%. Adding this new high-risk group to the established high-risk group of patients with a GRACE score ≥ 140 leads to a statistically significant increase of

Table 2 Patients' characteristics of patients reaching and not reaching the primary and secondary endpoints

Variable	Primary endpoint			Secondary endpoint		
	Survivors	Non-survivors	*p*	Survivors	Non-survivors	*p*
Number of patients	1793 (98.5%)	28 (1.5%)		1761 (96.7%)	60 (3.3%)	
Age (years)	60.5 ± 16.3	72.6 ± 11.6	<0.001	60.2 ± 16.3	74.7 ± 11.3	<0.001
Females	687 (38.3%)	8 (28.6%)	0.332	671 (38.1%)	24 (40%)	0.766
History of previous MI	331 (18.5%)	5 (17.9%)	0.469	326 (18.5%)	12 (20%)	0.905
Known congestive heart failure	237 (13.8%)	7 (25.0%)	0.587	239 (13.6%)	13 (21.7%)	0.107
Cardiovascular risk factors						
Hypertension	1091 (60.8%)	20 (71.4%)	0.686	1070 (60.8)	41 (68.3%)	0.735
Diabetes mellitus	332 (18.5%)	8 (28.6%)	0.397	317 (18.0%)	23 (39.0%)	<0.001
Hyperlipidemia	608 (33.9%)	7 (25%)	0.320	598 (33.9%)	17 (28.3%)	0.250
Smoking	376 (21.0%)	2 (7.1%)	0.157	374 (21.2%)	4 (6.7%)	0.008
Family history of CVD	354 (19.7%)	5 (17.9%)	1.00	354 (20.1%)	5 (8.3%)	0.017
History of PCI	461 (25.7%)	4 (14.3%)	0.196	454(25.9%)	11 (18.3%)	0.136
Risk factors						
DC (ms)	6.6 ± 2.9	2.9 ± 2.1	<0.001	6.7 ± 2.8	3.8 ± 2.5	<0.001
GRACE score (pts)	100 ± 33	146 ± 46	<0.001	99 ± 32	143 ± 39	<0.001

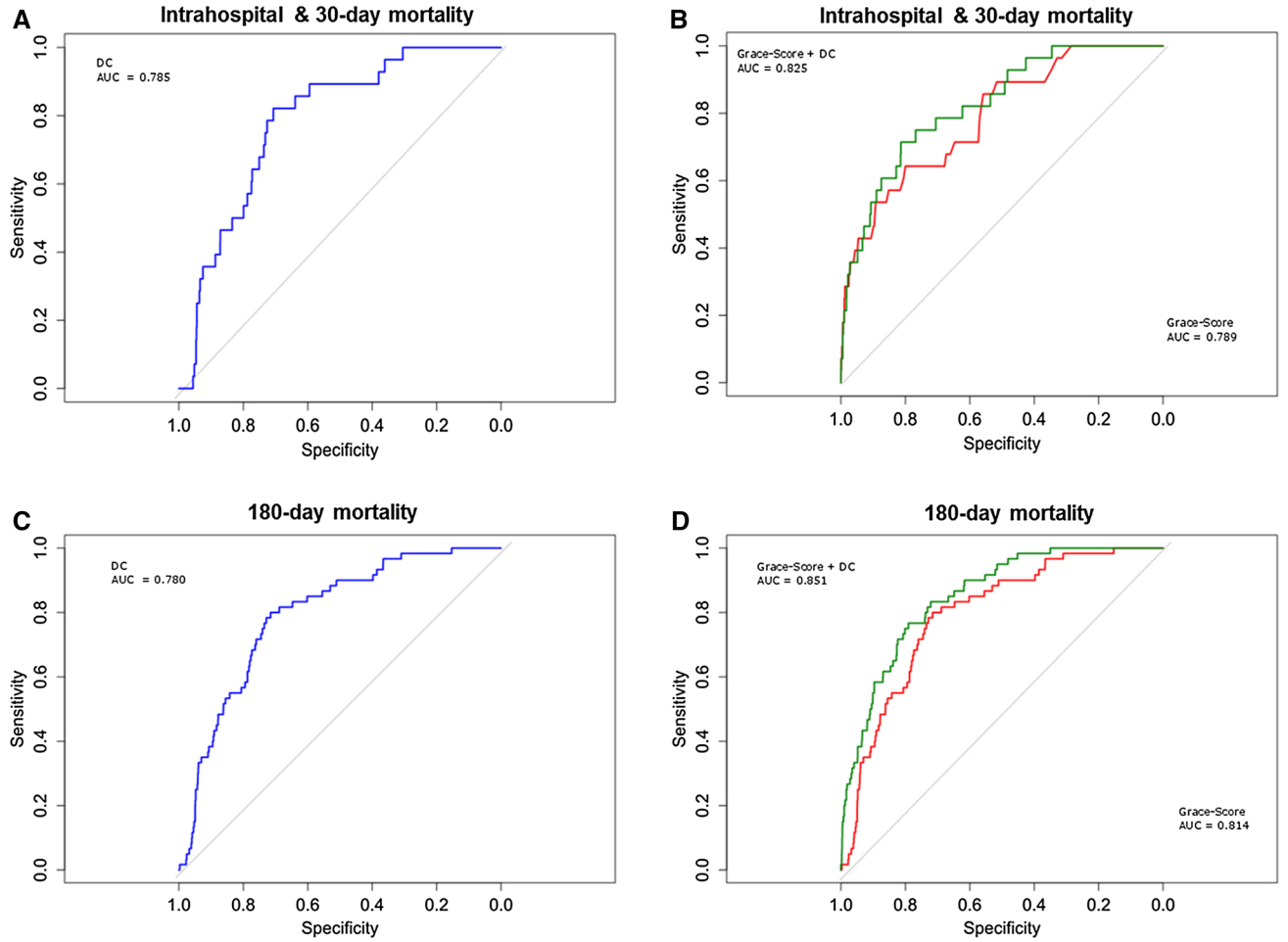

Fig. 2 Receiver–operator characteristic curves for prediction of the primary and secondary endpoints. **a, c** Deceleration capacity (DC), **b, d** GRACE score as well as the combination of the GRACE score and DC. The difference between the areas under the receiver-operator characteristic curve (AUC) of the GRACE score and the combination of the GRACE score and DC was highly significant for both endpoints ($p < 0.01$)

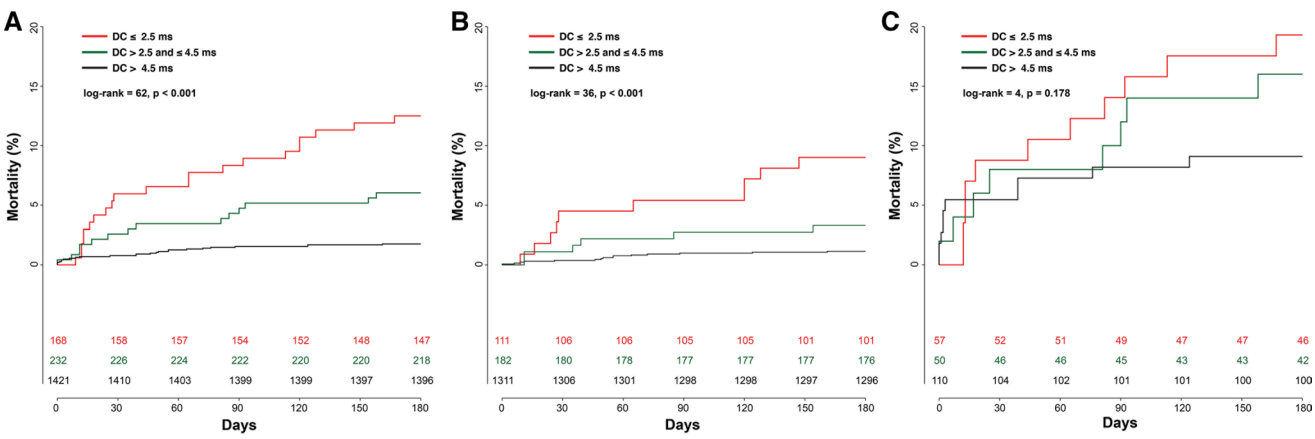

Fig. 3 Cumulative mortality rate of patients stratified by deceleration capacity (DC) ≤2.5, 2.5–4.5, and >4.5 ms, respectively. **a** Risk stratification in all patients, **b, c** risk stratification in patients with a GRACE score <140 and ≥140, respectively

Table 3 Uni- and multivariable analyses for prediction of intrahospital and 30-day mortality (primary endpoint)

Variable	Univariable analysis			Multivariable analysis		
	HR (95% CI)	*z*	*p*	HR (95% CI)	*z*	*p*
DC (per ms increase)	0.830 (0.774–0.889)	27.85	<0.001	0.806 (0.707–0.919)	10.33	<0.001
Age (per year increase)	1.060 (1.029–1.092)	14.57	<0.001	1.039 (1.006–1.073)	5.49	0.019
Creatinine (per mg/dl increase)	1.375 (1.179–1.604)	16.44	<0.001	1.329 (0.972–1.816)	3.18	0.075
Heart rate (per bpm increase)	1.005 (1.000-1.010)	4.54	0.033	1.006 (0.996–1.017)	1.39	0.238
Systolic blood pressure (per mmHG increase)	0.996 (0.980–1.012)	0.265	0.607			
Elevated cardiac enzyme levels (yes/no)	4.826 (2.283–10.202)	16.99	<0.001	3.405 (1.300-8.918)	6.22	0.013
ST-segment deviation (yes/no)	5.055 (2.334–10.951)	16.88	<0.001	3.410 (1.224–9.499)	5.51	0.019
Cardiac arrest at admission (yes/no)	56.808 (13.422-240.438)	30.11	<0.001	15.160 (0.583-394.284)	2.67	0.102
Kilip class (per class increase)	4.051 (2.483–6.607)	31.40	<0.001	1.965 (0.877–4.402)	2.69	0.101

Analyses were adjusted for betablocker treatment

bpm beats per minute, *DC* deceleration capacity, *HR* hazard ratio

Table 4 Uni- and multivariable analyses for prediction of 180-day mortality (secondary endpoint)

Variable	Univariable analysis			Multivariable analysis		
	HR (95% CI)	*z*	*p* value	HR (95% CI)	*z*	*p* value
DC (per ms increase)	0.823 (0.787–0.861)	71.51	<0.001	0.813 (0.746–0.886)	22.43	<0.001
Age (per year increase)	1.076 (1.053–1.100)	42.89	<0.001	1.060 (1.035–1.086)	22.19	<0.001
Creatinine (per mg/dl increase)	1.325 (1.169–1.500)	19.56	<0.001	1.266 (1.007–1.592)	4.07	0.044
Heart rate (per bpm increase)	1.005 (1.002–1.009)	9.878	0.002	1.006 (1.000–1.012)	4.13	0.042
Systolic blood pressure (per mmHG increase)	0.999 (0.988–1.010)	0.03	0.873			
Elevated cardiac enzyme levels (yes/no)	4.504 (2.708–7.491)	33.634	<0.001	2.942 (1.560–5.549)	11.12	0.001
ST-segment deviation (yes/no)	3.072 (1.712–5.510)	14.169	<0.001	1.588 (0.760–3.318)	1.51	0.219
Cardiac arrest at admission (yes/no)	54.724 (17.024–1775.915)	45.13	<0.001	57.224 (2.439–1342.663)	6.32	0.012
Kilip class (per class increase)	3.746 (2.599–5.401)	50.09	<0.001	1.915 (1.065–3.443)	4.72	0.03

Analyses were adjusted for betablocker treatment

bpm beats per minute, *DC* deceleration capacity, *HR* hazard ratio

Table 5 Sensitivity and positive predictive accuracy of high-risk groups for prediction of 180-day mortality

High-risk group	*n*	Sens	PPA
GRACE ≥ 140	217	48.3%	13.4%
GRACE ≥ 140 or DC ≤ 2.5 ms	328	65.0%	11.9%
p value		0.027	0.597

DC deceleration capacity, *GRACE* Global registry of acute coronary events score

sensitivity from 48.3 to 65.0% ($p = 0.027$) without affecting positive predictive accuracy ($p = 0.597$) (Table 5).

Discussion

The findings of our study indicate that in patients with suspected ACS point-of care testing of cardiac autonomic function by means of automatic assessment of short-term DC yields important prognostic information on top of established risk markers. DC significantly improves risk assessment by the GRACE score with respect to prediction of early and late mortalities. Predictive value of DC is particularly strong in patients with a GRACE score < 140 in whom impaired DC (≤2.5 ms) identifies a relevant new high-risk group of patients. Adding this new high-risk group to the established high-risk group with a GRACE score ≥ 140 increases sensitivity by 35% without affecting positive predictive accuracy.

Many studies demonstrated the strong prognostic value of cardiac autonomic dysfunction in cardiac patients [10]. The strongest evidence exists for patients after myocardial infarction in whom depressed autonomic function predicts increased risk of subsequent death independently from left ventricular ejection fraction, arrhythmias, and demographic factors [7, 9, 17, 18]. In most studies, cardiac autonomic function was assessed from ECG- or blood pressure recordings that have been either obtained under strictly standardized conditions, over prolonged period of time (e.g., 24 h) or in the chronic phase of myocardial infarction [10]. The signal processing technology employed in the present study allows for an automated point-of-care assessment of cardiac autonomic function within minutes after hospital admission and thus opens new perspectives for bedside risk stratification in the acute clinical setting. This type of risk assessment is objective and can be carried out in a standardized manner. There is no need for elaborate training of personnel, such as for echocardiography and its further development [19]. In addition, the method might circumvent gender-specific aspects that play a role in the diagnosis of ACS [20, 21].

In contrast to most previous studies, cardiac autonomic function was assessed in patients with potential myocardial ischemia prior to any revascularization procedure. Only very few studies studied cardiac autonomic function in the very acute phase of myocardial infarction. Bonnemeier et al. analyzed heart rate turbulence and heart rate variability in patients with acute myocardial infarction by starting Holter recordings directly after hospital admission [22, 23]. Both heart rate turbulence and variability were initially depressed but recovered after successful reperfusion. In a small study by Sade et al. including 126 patients, heart rate turbulence assessed in the acute phase of myocardial infarction was a strong and independent predictor of 1-year mortality [24]. The results of our study further strengthen the important prognostic role of cardiac autonomic function assessed in the acute phase of myocardial ischemia.

Importantly, the strong prognostic meaning of cardiac autonomic function is not restricted to patients admitted to the ED for suspected ACS. In a previous study, we could demonstrate that impaired DC was also a strong and independent predictor of early and late mortality in 2303 non-cardiac patients [13], making DC also particularly useful as screening test in emergency patients in whom the diagnosis is primarily unclear.

Our study also re-evaluates the strong prognostic value of the GRACE score in a contemporary treated population with suspected ACS. In our study, the GRACE score yielded large AUCs of 78.8 and 81.4% for prediction of early and 180-mortality, which is in line with previous findings from large registries. In a study by Granger et al. including 27,503 patients with ACS, the GRACE score yielded an AUC of 83% for prediction of intrahospital mortality [2]. In a study by Fox et al. including 43,810 patients with ACS, the GRACE score yielded an AUC of 81% for prediction of 180-day mortality [25]. Despite the strong predictive value of the GRACE score, DC significantly improved its risk predictive power by significantly improving C-statistics and NRI.

Our study might have important clinical implications for management of patients with suspected ACS. According to the current guidelines, patients with suspected or confirmed ACS and a GRACE score <140 are considered to be at low- or intermediate risk [1, 26], which has direct implications for their clinical management. Thus, the current ESC guidelines recommend early discharge of patients with suspected ACS and a GRACE score <140, if high sensitive troponins are sequentially below the upper limit of normal, the patient is pain free and differential diagnoses are excluded [1]. Moreover, the GRACE score is also recommended to guide invasive strategies in Non-ST-elevation ACS, with a GRACE score ≥ 140 being a high-risk criterion mandating an early invasive strategy (<24 h) [1]. Finally, the GRACE score is the recommended tool to predict outcome after hospital discharge. In our study, DC significantly improved risk assessment by the GRACE score. Among the 1,604 patients with a GRACE score <140, DC ≤ 2.5 ms identified a new high-risk group of 111 patients, whose prognosis was not statistically different to that of patients with GRACE ≥ 140. These patients should, therefore, be considered as high-risk patients. Future studies should test whether ACS patients with DC ≤ 2.5 ms benefit from intensified monitoring and early invasive treatment.

The limitations of our study need to be recognized. First, the findings of our study should be independently validated. Second, compared to the large-scale studies on the GRACE score [2, 25, 27], the sample size our study is limited. However, in contrast to the GRACE score, retrospective application of DC to large ACS registries for validation is impossible. Third, for methodological reasons, DC can only be assessed in patients with sinus rhythm. It is known that ACS patients with atrial fibrillation or other non-sinus rhythms are at increased risk [28]. Fifth, we assessed DC only at hospital admission. It is presently unknown whether DC assessed prior to hospital discharge might be a better predictor of late mortality.

Sixth, the addition of LVEF might improve risk assessment in addition to DC and the GRACE score. In our study, however, LVEF was not routinely assessed at hospital admission.

Finally, as our study is purely observational, it is unknown whether a different treatment based on an improved risk assessment by DC translates into a better outcome.

Conclusions

In conclusion, automated point-of-care assessment of cardiac autonomic function by means of DC is feasible and provides strong and independent prognostic information in patients with suspected ACS. DC significantly improves the GRACE score, which is considered as gold standard for risk assessment in ACS patients. The technology is inexpensive, readily available, and can be implemented in existing monitoring devices and DC could be calculated within minutes. Future studies should test whether implementing DC into clinical decision making improves patient care.

Compliance with ethical standards

Conflict of interest None.

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Sympathetic activity–associated periodic repolarization dynamics predict mortality following myocardial infarction

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***Background*. Enhanced sympathetic activity at the ventricular myocardium can destabilize repolarization, increasing the risk of death. Sympathetic activity is known to cluster in low-frequency bursts; therefore, we hypothesized that sympathetic activity induces periodic low-frequency changes of repolarization. We developed a technique to assess the sympathetic effect on repolarization and identified periodic components in the low-frequency spectral range (≤0.1 Hz), which we termed periodic repolarization dynamics (PRD).**

***Methods*. We investigated the physiological properties of PRD in multiple experimental studies, including a swine model of steady-state ventilation (n = 7) and human studies involving fixed atrial pacing (n = 10), passive head-up tilt testing (n = 11), low-intensity exercise testing (n = 11), and beta blockade (n = 10). We tested the prognostic power of PRD in 908 survivors of acute myocardial infarction (MI). Finally, we tested the predictive values of PRD and T-wave alternans (TWA) in 2,965 patients undergoing clinically indicated exercise testing.**

***Results*. PRD was not related to underlying respiratory activity (P < 0.001) or heart-rate variability (P = 0.002). Furthermore, PRD was enhanced by activation of the sympathetic nervous system, and pharmacological blockade of sympathetic nervous system activity suppressed PRD (P ≤ 0.005 for both). Increased PRD was the strongest single risk predictor of 5-year total mortality (hazard ratio 4.75, 95% CI 2.94–7.66; P < 0.001) after acute MI. In patients undergoing exercise testing, the predictive value of PRD was strong and complementary to that of TWA.**

***Conclusion*. We have described and identified low-frequency rhythmic modulations of repolarization that are associated with sympathetic activity. Increased PRD can be used as a predictor of mortality in survivors of acute MI and patients undergoing exercise testing.**

***Trial registration*. ClinicalTrials.gov NCT00196274.**

***Funding*. This study was funded by Angewandte Klinische Forschung, University of Tübingen (252-1-0).**

Introduction

Sudden cardiac death (SCD) is the single most common cause of death in the industrialized world (1). A substantial proportion of SCD cases occur in patients after myocardial infarction (MI). Randomized trials have demonstrated that in high-risk patients after MI, mortality can be effectively reduced by prophylactic implantation of a cardioverter-defibrillator (ICD) (2). Consequently, identification of high-risk individuals is a major objective in cardiology. Current guidelines recommend the assessment of left ventricular ejection fraction (LVEF) as the gold standard risk predictor (3, 4); however, this approach lacks both sensitivity and specificity (1, 5). Therefore, development of novel risk markers is of great clinical interest.

Assessment of repolarization instability may more directly estimate the risk of fatal cardiac arrhythmias (6). It is well known from experimental and clinical studies that enhanced sympathetic activity is a key factor leading to the destabilization of myocardial repolarization (7–14). However, without directly recording neural activity, which is impractical in the clinical setting, assessment of the sympathetic effect on myocardial repolarization has not been possible to date. As sympathetic activity is organized in a series of low-frequency bursts (15–19), we postulated that repolarization changes induced by the sympathetic nervous system would exhibit low-frequency periodic features.

In the present study, we propose what we believe is a novel way to assess the sympathetic effect on cardiac repolarization. We developed a technology and uncovered periodic components of repolarization in the low-frequency spectral range (≤0.1 Hz), which we termed periodic repolarization dynamics (PRD). The first part of

Conflict of interest: The authors have declared that no conflict of interest exists.
Citation for this article: *J Clin Invest.* 2014;124(4):1770–1780. doi:10.1172/JCI70085.

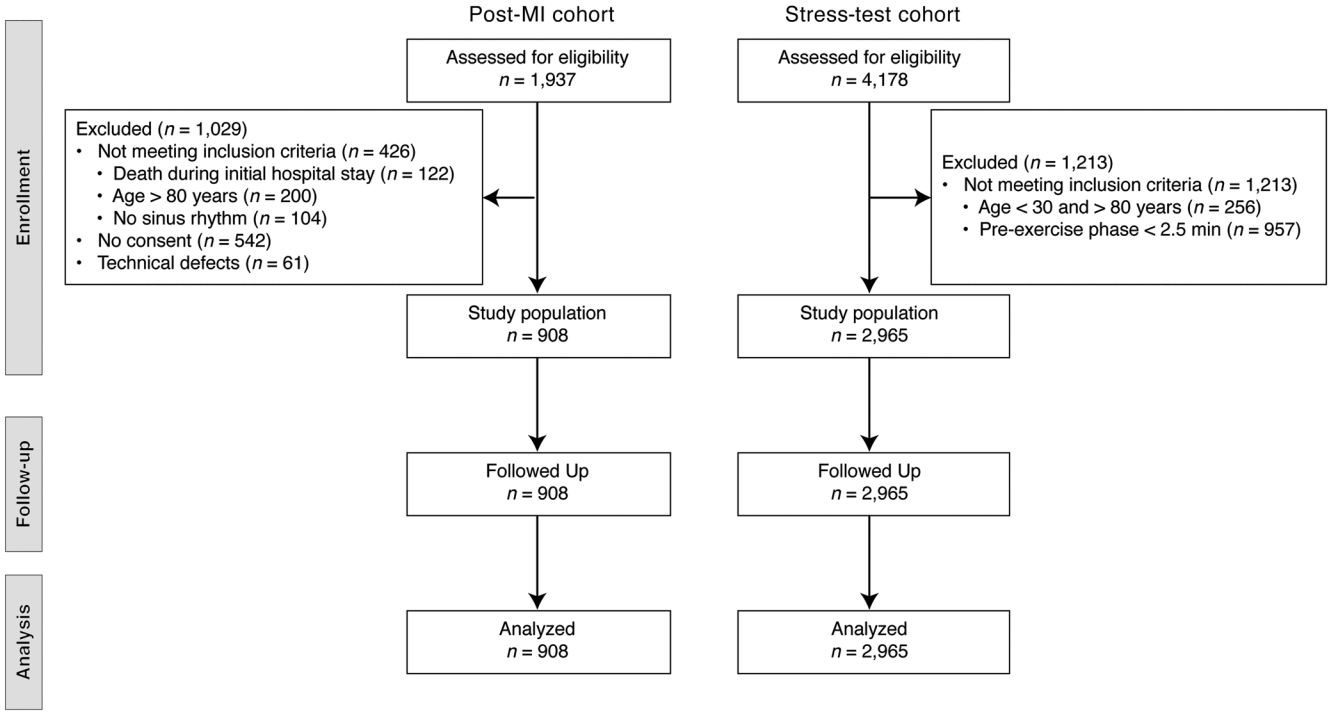

Figure 1
CONSORT flow diagrams. Enrollment, follow-up, and analysis in the post-MI and stress-test cohorts.

this article focuses on the physiological properties of PRD, including activation and blockade of the sympathetic nervous system. In the second part of this investigation, we assess the prognostic meaning of enhanced PRD in patients surviving acute MI (post-MI cohort; Figure 1A) and patients undergoing clinically indicated exercise testing (stress-test cohort; Figure 1B). In the stress-test cohort we also tested the prognostic meaning of exercise-induced T-wave alternans (TWA), which is presently considered to be the strongest existing marker of repolarization instability.

Results

Repolarization is subject to low-frequency periodic modulations. We developed a technique to dynamically track repolarization dynamics and to quantify their periodic components. Details of the methodology are reported in Methods. Briefly, we used standard, high-resolution, surface ECG recorded in or converted to the orthogonal Frank lead configuration. As electrocardiographic repolarization is a phenomenon occurring in both space and time, we integrated the spatiotemporal information of each T-wave into a single vector, $T°$. We used the angle $dT°$ between successive repolarization vectors as an estimate of the instantaneous repolarization instability (Figure 2, A–C). We observed characteristic low-frequency oscillations in $dT°$ in health and disease (Figure 2D). In order to quantify these low-frequency (≤0.1 Hz) periodic patterns, we employed wavelet analysis (Figure 2E).

PRD is not an epiphenomenon of underlying heart rate variability. We tested whether PRD was present in the absence of heart rate variability (HRV). We studied 10 individuals (median age 52 [interquartile range (IQR) 32] years, 5 females), who underwent a clinically indicated electrophysiological (EP) study at our institution. Patient characteristics are provided in Methods. We compared 5-minute episodes of spontaneous sinus rhythm to 5-minute episodes during fixed atrial stimulation, which was set above the spontaneous heart rate. Fixed atrial pacing almost abolished HRV ($P < 0.001$; Supplemental Table 1; supplemental material available online with this article; doi:10.1172/JCI70085DS1), but exerted only minimal, non-significant effects on PRD (ratio of PRD after provocation to PRD before provocation [PRD ratio] 0.75, 95% CI 0.50–1.17, $P = 0.193$; Figure 3A, Supplemental Figure 1A, and Supplemental Table 1).

PRD is not an epiphenomenon of underlying respiratory activity. To test whether PRD was present in the absence of spontaneous breathing, we performed an experimental study in a swine model. Seven female domestic pigs were mechanically ventilated and sedated with α-chloralose, which has been shown to induce only minimal effects on the cardiac autonomic nervous system (20). Respiratory frequency and tidal volume were maintained constant by means of volume-controlled ventilation. Details of the experimental design are provided in Methods. PRD occurred independently of respiratory activity, as illustrated in Figure 4A. There was no interference between respiratory activity and PRD in any animal, as confirmed by spectral and crossspectral analysis (Figure 4, B and C; median coherence 0.044 [IQR 0.026]; $P < 0.001$ for the difference from the threshold of 0.5).

PRD is enhanced by sympathetic activation and suppressed by sympathetic blockade. We tested the effects of sympathetic activation on PRD in 11 healthy male volunteers (median age 24 [IQR 3] years). Sympathetic activation was achieved by means of head-up tilt testing and low-intensity exercise. Both tilt-table testing (PRD ratio 1.80, 95% CI 1.35–2.58, $P = 0.005$; Figure 3B, Supplemental Figure 1B, and Supplemental Table 1) and low-intensity exercise (PRD ratio 3.85, 95% CI 2.49–5.61, $P = 0.001$; Figure 3C, Supplemental Figure 1B, and Supplemental Table 1) led to substantial enhancement of PRD.

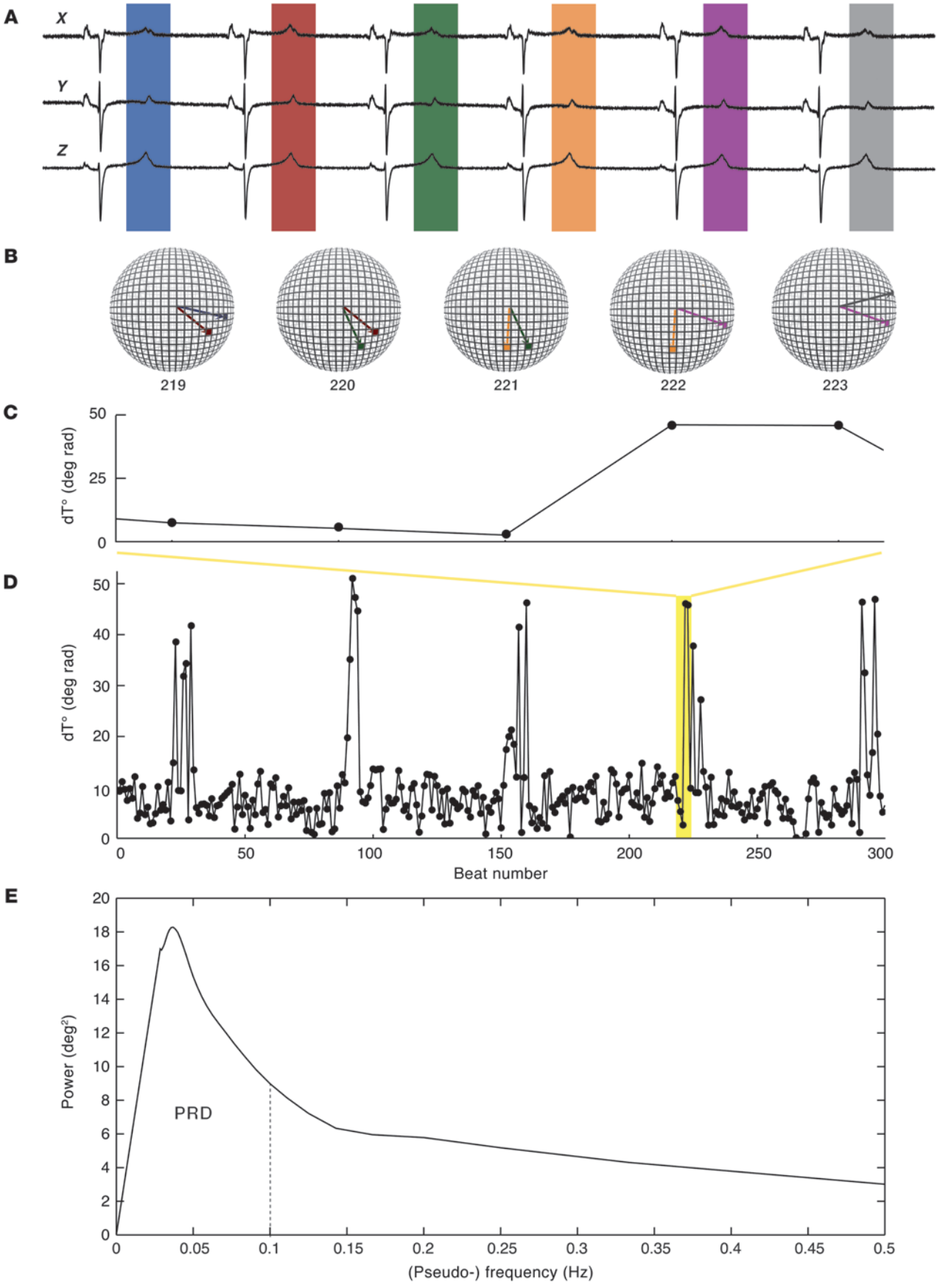

Figure 2
Assessment of PRD. (**A**) Illustration of the weight-averaged vector of repolarization (T°) for each T-wave from surface ECG recorded in the Frank leads configuration. (**B**) Three-dimensional visualization of successive T° vectors projected into virtual spheres. The angle dT° between successive repolarization vectors was used as an estimate of instantaneous repolarization instability. (**C** and **D**) The dT° signal exhibits characteristic low-frequency oscillations. **C** shows dT° values for beats #219-223, corresponding to the spheres in **B**. (**E**) Quantification of PRD using wavelet analysis. PRD was defined as the average wavelet coefficient corresponding to frequencies of 0.1 Hz or less.

Conversely, we tested the effects of antiadrenergic intervention in 10 patients (median age 57 [IQR 21] years, 7 females) undergoing an EP study at our institution. Antiadrenergic intervention was achieved by pharmacological beta blockade. The diagnostic protocol is described in Methods. Beta blockade caused a striking suppression of PRD in all patients (PRD ratio 0.41, 95% CI 0.28–0.61, P = 0.002; Figure 3D, Supplemental Figure 1C, and Supplemental Table 1).

For comparison, the effects of sympathetic activation and blockade on the low-frequency component of heart-rate variability are shown in Supplemental Table 1.

Increased PRD predicts total and cardiovascular mortality after MI. We tested the prognostic significance of PRD in a cohort of 908 patients from the Autonomic Regulation Trial (median age 61 [IQR 17] years, 174 females) who survived an acute MI (Figure 1A and Table 1) (21, 22). Sixty-nine patients died within the first 5 years of follow-up. Representative resting dT° signals in a patient who survived the follow-up period and in a patient who suddenly died 8 months after index MI are depicted in Figure 5, A and B, respectively. Although low-frequency oscillations in dT° were evident in both patients, the amplitudes of PRD were much higher in the nonsurviving patient. The level of PRD was significantly associated with 5-year mortality (6.67 [IQR 8.58] deg^2 vs. 2.66 [IQR 3.93] deg^2; P < 0.001). For subsequent survival analyses, we dichotomized PRD at the upper quartile of the study population. The 227 patients with PRD greater than or equal to 5.75 deg^2 (Figure 5C) had a 5-year risk of death of 18.2% compared with 4.1% in the 681 patients with PRD of less than 5.75 deg^2 (P < 0.001). Both uni- and multivariable analyses for the prediction of 5-year total mortality indicated that PRD greater than or equal to 5.75 deg^2 was the strongest single risk predictor in the study cohort (Table 2 and Supplemental Figure 2). The predictive value of PRD greater than or equal to 5.75 deg^2 was independent of that of established risk markers, including reduced LVEF of 35% or less (3, 4), the Global Registry of Acute Coronary Events (GRACE) score (23), the presence of diabetes mellitus, elevated mean heart rate, reduced HRV, and increased QT variability index (QTVI) (24). Subsequently, we assessed the incremental prognostic value of PRD to established risk-prediction models (Supplemental Table 2). PRD significantly improved all tested risk-prediction models based on the combination of LVEF, GRACE score, respiratory rate, and HRV parameters. Subgroup analyses revealed that increased PRD was a particularly strong predictor of mortality in the 179 post-MI patients who also suffered from diabetes mellitus, identifying a group of 179 patients with a cumulative 5-year mortality rate of 38.8% (Figure 5D).

Finally, we also investigated whether PRD predicted cardiovascular mortality. Of the 69 deaths, 36 were cardiovascular deaths. As shown in Table 2, PRD greater than or equal to 5.75 deg^2 was also a strong and independent predictor of 5-year cardiovascular mortality.

The predictive value of PRD is complementary to that of exercise-induced TWA. To test the predictive values of PRD and TWA, we studied 2,965 patients (median age 57 [IQR 16] years, 1,187 females) from the Finnish Cardiovascular Study (median age 57 [IQR 16], 1,187 females; Figure 1B and Table 1) who underwent a clinically indicated exercise test (25). During a median follow-up of 6 years, 309 patients died. In all patients, TWA was measured during exercise by the modified moving average (MMA) method (25–27). PRD was assessed in the preexercise period with patients sitting on a bicy-

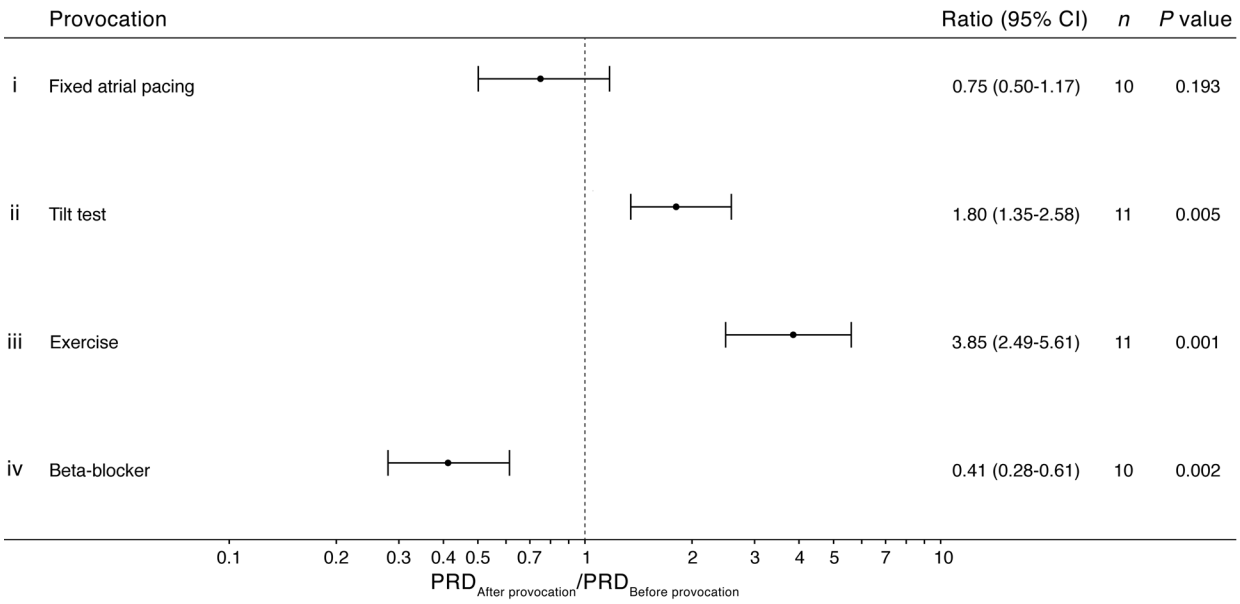

Figure 3
Physiological and pharmacological provocations. Effects of fixed atrial stimulation (i), tilt-table testing (ii), exercise (iii), and pharmacological beta blockade (iv) on PRD. PRD ratio was plotted on a logarithmic axis and used to quantify the effect of each procedure.

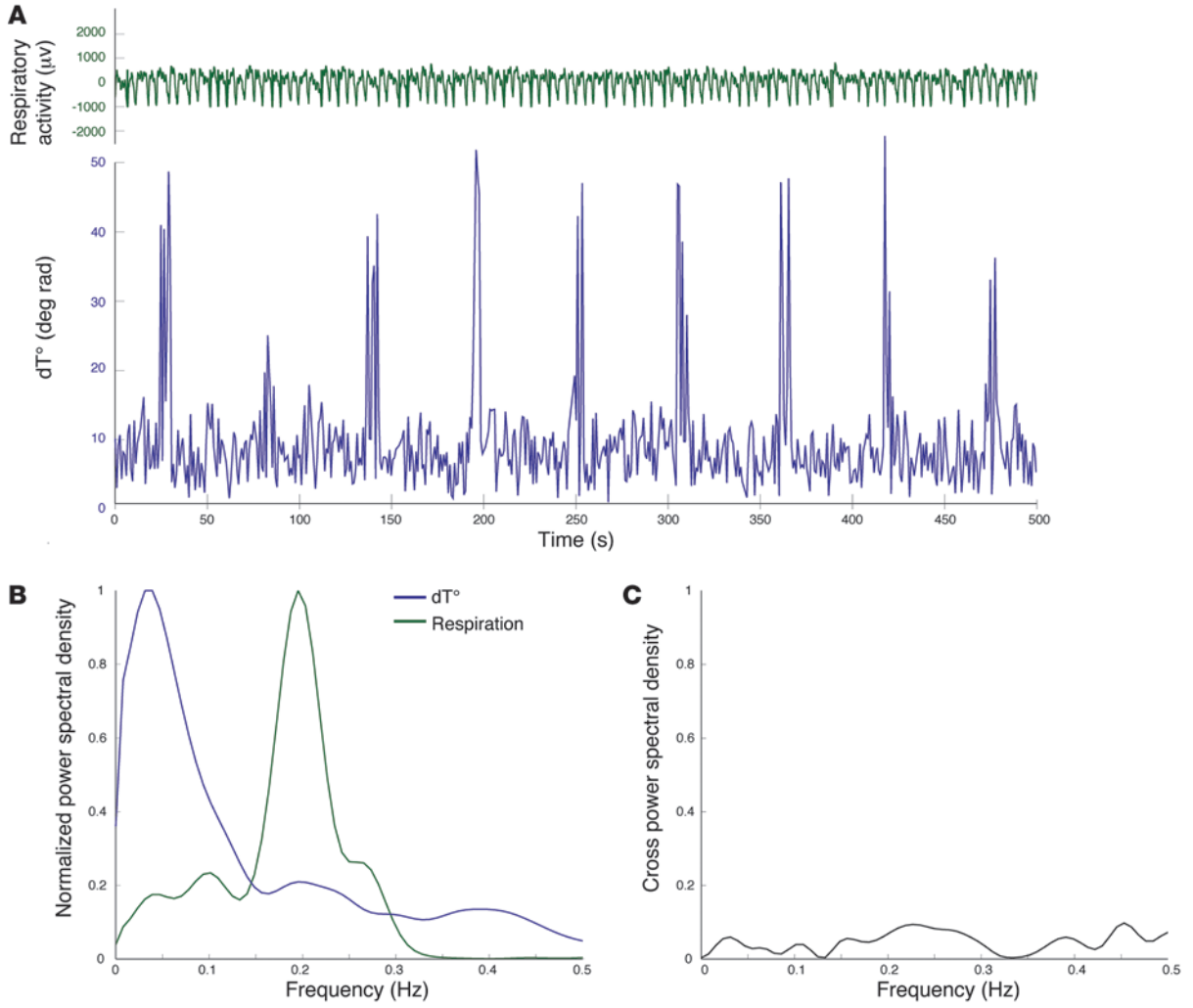

Figure 4
Effect of respiration on PRD in a volume-controlled ventilated swine. (**A**) Signals of respiratory activity (green) and *dT*° (blue). Respiratory activity was recorded by a piezoelectric thoracic sensor. The *dT*° signal exhibits typical low-frequency oscillations occurring independently from respiratory activity. (**B**) Spectral analysis of respiratory activity and the *dT*° signal. Power spectra were normalized by their maximum value. (**C**) Cross-spectral analysis of respiratory activity and the *dT*° signal showing a lack of interference between both signals.

cle ergometer. As expected, PRD levels in this cohort were higher than those in the post-MI cohort, where PRD was estimated in the supine resting position (9.2 [IQR 13.37] deg² vs. 2.82 [IQR 4.34] deg², respectively; $P < 0.001$). Both PRD and TWA were significantly associated with mortality (8.96 [IQR 13.23] deg² vs. 12.04 [IQR 16.32] deg², $P < 0.001$, and 23.00 [IQR 15] μV vs. 26.00 [IQR 17] μV, $P < 0.001$, respectively). Univariable Cox regression analysis showed that both markers were strong predictors of total mortality (standardized coefficients 0.203, 95% CI 0.113–0.293, $P < 0.001$ for PRD; and 0.256, 95% CI 0.164–0.348, $P < 0.001$ for TWA). This remained true on multivariable analysis, which also included age, sex, previous MI, presence of diabetes mellitus, and treatment with beta-blockers (Table 3). The significant crossterm between TWA and PRD (TWA × PRD) indicated that the relationship between the outcome and one predictor was dependent on the levels of the other predictor. We therefore tested the additive prognostic value of PRD for different levels of TWA. As illustrated in Supplemental Figure 3, PRD provided incremental prognostic information at all levels of TWA.

Of the 309 deaths, 138 were cardiovascular deaths. Increased preexercise PRD was also a significant predictor of cardiovascular mortality in univariable (standardized coefficient 0.256, 95% CI 0.126–0.385; $P < 0.001$) and multivariable analysis (Table 3).

Discussion

In the present study, we identified periodic oscillations of repolarization that were localized in the low-frequency spectral range and were detectable by conventional surface ECG. PRD was evident in health and disease without provocations and occurred autonomously from underlying HRV and respiratory activity. PRD was augmented by physiological provocations leading to activation of the sympathetic nervous system and was suppressed by pharmacological adrenergic blockade. Increased PRD obtained under resting conditions was a very strong predictor of total and cardiovascular mortality in survivors of acute MI and patients undergoing a clinically indicated exercise test. The prognostic value of PRD was incremental to that of established risk markers, including LVEF and TWA.

Table 1
Patient characteristics and treatment in the post-MI and stress-test cohorts

	Post-MI cohort	Stress-test cohort
Study characteristics		
Number of patients, *n*	908	2,965
Median follow-up (IQR), months	60 (0)	75.1 (47.7)
Total deaths, *n* (%)	69 (7.6)	309 (10.4)
Cardiovascular deaths, *n* (%)	36 (4.0)	138 (4.7)
Patient characteristics		
Median age (IQR), years	61 (17)	57 (16)
Females, *n* (%)	174 (19.2)	1187 (40.0)
Diabetes mellitus, *n* (%)	179 (19.7)	344 (11.6)
History of previous MI, *n* (%)	86 (9.5)	552 (18.6)
Median LVEF (IQR), %	53 (15)	66 (16)
Known CAD (%)	908 (100)	883 (29.8)
Treatment		
PCI, *n* (%)	848 (93.4)	NA
Thrombolysis, *n* (%)	13 (1.4)	NA
CABG, *n* (%)	6 (0.7)	NA
Beta blockers, *n* (%)	864 (95.1)	1709 (57.6)

CABG, coronary artery bypass graft; CAD, coronary artery disease; NA, not available; PCI, percutaneous coronary intervention.

Noninvasive assessment of the sympathetic effect on myocardial repolarization is of great clinical interest. A wealth of evidence supports the widely held belief that increased sympathetic nervous system activity is associated with increased cardiac vulnerability (11–14). In human subjects, noninvasively measured parameters, including HRV and baroreflex sensitivity, have been employed to study sympathetic activity under routine clinical conditions (28). This approach is based on the principle that activation of the sympathetic nervous system evokes several physiological effects, including increasing systolic contractility rate and vasomotor tone as well as accelerating heart rate and atrioventricular conduction (10). However, these measurements provide only an indirect probe of the sympathetic effect on repolarization; they reflect influences on the sinoatrial node and blood vessels, not on the ventricular myocardium.

At the level of cardiomyocytes, stimulation of β-adrenergic receptors alters intracellular calcium dynamics (28) and shortens action potential duration (10). Importantly, the effect of sympathetic stimulation on the 3 cell types of the ventricular myocardium (epicardial cells, M cells, and endocardial cells) is nonuniform (29, 30). Adrenergic activation abbreviates the action potential duration of epicardial and endocardial cells to a greater degree than the action potential duration of M cells (31), leading to an increased transmural dispersion of repolarization (28).

It is well known that sympathetic activity is organized in series of low-frequency bursts (15–19). We therefore assumed that phasic sympathetic activation induces phasic changes in repolarization localized in the low-frequency spectral range, and we developed a method to track the sympathetic effect on transmural dispersion of repolarization. Our findings confirmed this hypothesis. For what we believe is the first time, we detected periodic changes in repolarization in the same range as those of the sympathetic nervous system. PRD was significantly enhanced by sympathetic activation and was substantially suppressed by sympathetic blockade. Moreover, increased PRD was a strong predictor of total and cardiovascular mortality, which is in line with the results of many studies showing that enhanced sympathetic activity is associated with an increased risk of death (11–14).

In particular, increased PRD was identified as the strongest single risk predictor of total and cardiovascular mortality in a large cohort of post-MI patients. The predictive value of PRD was independent of established risk markers. PRD substantially improved several multivariable models in prediction of total mortality, confirming its incremental prognostic value. The mechanism by which PRD identifies high-risk patients significantly differs from that of structural markers such as LVEF. Directly estimating sympathetic activity at the level of myocardial repolarization may provide more accurate information on cardiac risk. Post-MI patients with increased PRD had a very poor prognosis when they also suffered from diabetes mellitus. Both MI (32) and diabetes mellitus (33) are characterized by spatially heterogeneous sympathetic innervation, which is associated with negative prognosis (10).

We tested the prognostic significance of PRD in a large cohort of patients undergoing clinically indicated exercise testing. Increased PRD was a strong predictor of total and cardiovascular mortality and provided incremental prognostic information to that of exercise-induced TWA. This indicates that PRD can be used to detect high-risk patients who are not identified by TWA. The complementary prognostic information provided by PRD and TWA implies that these 2 markers capture different aspects of repolarization instability. While PRD most probably reflects low-frequency oscillations related to sympathetic activity, TWA is mainly caused by high-frequency action potential oscillations provoked by abnormal calcium handling (34). TWA is an important predictor of cardiovascular mortality, including sudden death (6, 27, 35, 36). However, it needs to be provoked by exercise (37) or invasive procedures (38). Assessment of PRD is inexpensive, easily obtainable under resting conditions, and noninvasive and significantly improves available risk-stratification strategies.

Our study has several limitations. First, high-resolution ECG is required in order to measure PRD. It remains to be demonstrated whether our results are reproducible with lower-resolution tracings. Second, in both cohorts, risk markers were only assessed at enrollment. Therefore, we cannot comment on the immediate and long-term reproducibility of PRD as well as the effect of treatment on PRD. Third, the prognostic value of PRD needs to be validated in independent cohorts. Fourth, as PRD is dependent on the patient's body position and activity level, the proposed cutoff value is only valid for recordings obtained in the supine resting position. Fifth, we confirmed the prognostic value of PRD for prediction of total mortality and cardiovascular mortality. Although it is plausible to assume that increased levels of PRD are also associated with arrhythmic mortality, this needs to be tested in future studies. Finally, although we have shown that increased PRD is a powerful risk predictor, we have no data to show that specific treatments based on the use of this predictor will improve patient outcome.

In conclusion, PRD constitutes an electrocardiographic phenomenon that most likely reflects the myocardial response to sympathetic activation. Increased PRD is a potent risk predictor

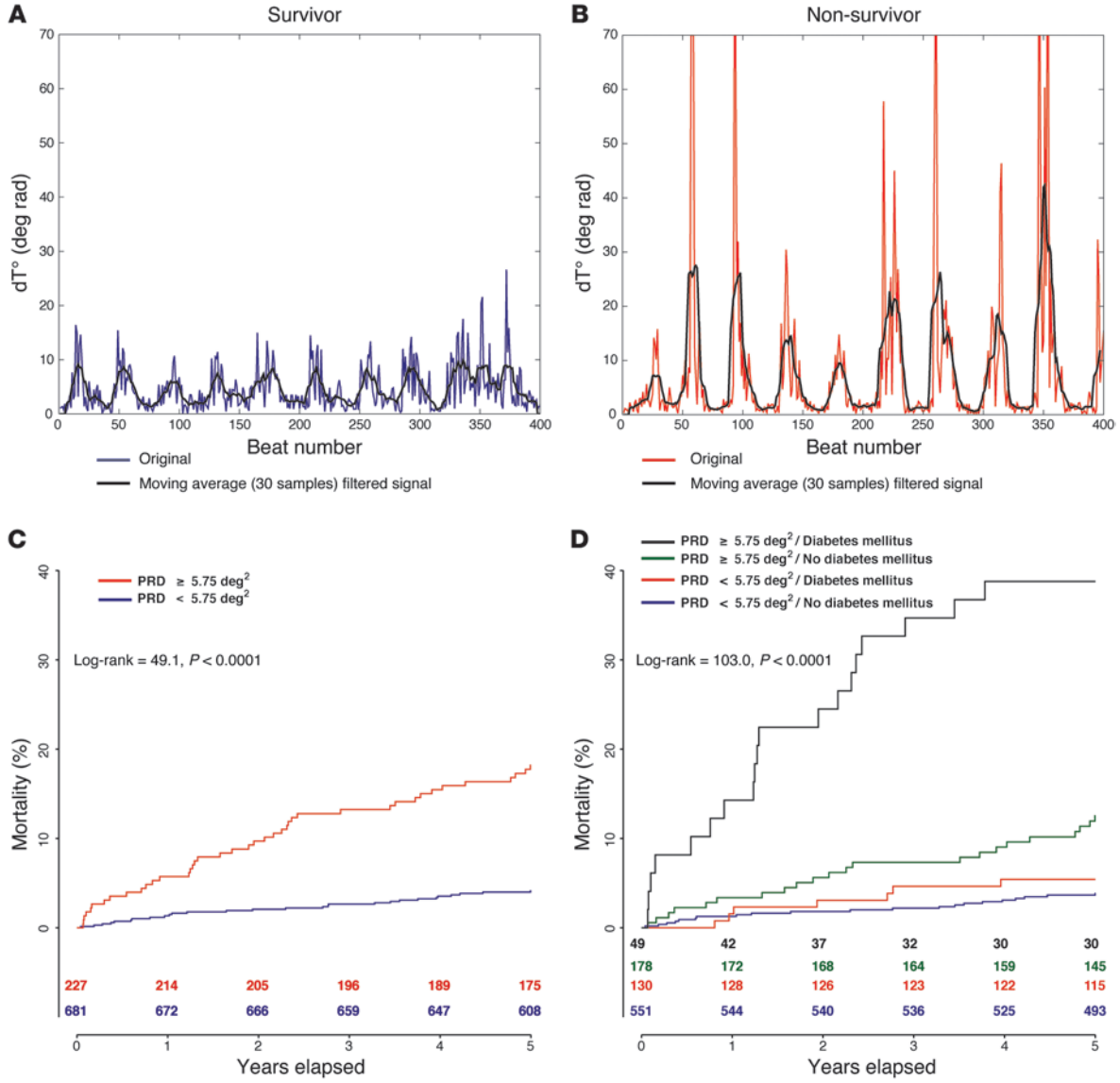

Figure 5
PRD in post-MI patients. (**A**) Typical *dT°* signal (blue line) obtained from a 50-year-old post-MI patient who survived the 5-year follow-up period. The signal shows characteristic low-frequency oscillations. For better illustration of these oscillations, a low-pass filter was applied and plotted on top of the original signal (black line). (**B**) Typical *dT°* signal (red line) from a 75-year-old post-MI patient who suddenly died 8 months after MI. Compared with the survivor, the amplitude of PRD was substantially enhanced. (**C**) Cumulative mortality rates of patients stratified by PRD of 5.75 deg² or more. (**D**) Cumulative mortality rates of patients stratified by PRD of 5.75 deg² or more and presence of diabetes mellitus.

of total and cardiovascular mortality, and its use significantly improves established risk-stratification concepts. Future studies are needed to test whether high-risk patients identified by PRD benefit from prophylactic therapies.

Methods

Participants. The physiological properties of PRD were studied in 3 cohorts at the University Hospital of Tübingen. We tested the effects of fixed atrial pacing (atrial-pacing cohort) in 10 individuals (median age 52 [IQR 42] years, 5 females) undergoing a clinically indicated diagnostic EP study. Indications for EP studies were paroxysmal supraventricular tachycardia in 7 patients and evaluation of unexplained syncope in 3 patients. We investigated the effect of beta blockade in 10 patients (median age 57 [IQR 21] years, 7 females) undergoing an EP study for paroxysmal supraventricular tachycardia (adrenergic-blockade cohort). In both EP studies, all patients were in sinus rhythm, had normal LVEF, were not suspected of suffering from coronary artery disease, and had no significant valve stenosis or insufficiency on echocardiography. We also studied the effects of passive head-up tilt and low-intensity exercise in 11 healthy male volunteers (median age 24 [IQR 3] years, adrenergic-activation cohort).

The prognostic power of PRD was tested in 908 survivors (median age 61 [IQR 17] years, 174 females) of acute MI (post-MI cohort; Figure 1A and Table 1) and 2,965 patients (median age 57 [IQR 16] years, 1,187 females) undergoing clinically indicated exercise testing (stress-test cohort; Figure

Table 2
Univariable and multivariable association of risk markers with 5-year all-cause and cardiovascular mortality in 908 survivors of acute MI (post-MI cohort)

	All-cause mortality			
Risk variable	**Univariable Cox regression**		**Multivariable Cox regression**	
	Hazard ratio (95% CI)	***P* value**	**Hazard ratio (95% CI)**	***P* value**
LVEF ≤ 35%	3.81 (2.23 to 6.51)	<0.001	2.13 (1.22 to 3.70)	0.008
GRACE[A] score ≥120	5.54 (3.24 to 9.46)	<0.001	3.61 (2.06 to 6.31)	< 0.001
Diabetes mellitus	2.61 (1.61 to 4.23)	<0.001	2.07 (1.25 to 3.41)	0.005
Mean HR > 75 bpm	1.98 (1.11 to 3.55)	0.020	1.10 (0.56 to 2.17)	0.783
SDNN ≤ 70 ms	2.01 (1.22 to 3.33)	0.007	1.71 (0.96 to 3.07)	0.072
QTVI > –0.47	2.54 (1.55 to 4.19)	<0.001	1.12 (0.65 to 1.93)	0.688
PRD ≥ 5.75 deg^2	4.75 (2.94 to 7.66)	<0.001	3.03 (1.79 to 5.11)	<0.001
	Cardiovascular Mortality			
Risk variable	**Univariable Cox regression**		**Multivariable Cox regression**	
	Hazard ratio (95% CI)	***P* value**	**Hazard ratio (95% CI)**	***P* value**
LVEF ≤ 35%	4.69 (2.32 to 9.50)	< 0.001	2.71 (1.30 to 5.67)	0.008
GRACE[A] score ≥120	5.82 (2.75 to 12.33)	< 0.001	3.80 (1.73 to 8.35)	< 0.001
Diabetes mellitus	2.72 (1.40 to 5.31)	0.003	2.16 (1.08 to 4.31)	0.029
Mean HR > 75 bpm	2.22 (1.02 to 4.86)	0.046	1.36 (0.55 to 3.38)	0.510
SDNN ≤ 70 ms	1.89 (0.93 to 3.82)	0.080	1.48 (0.65 to 3.36)	0.350
QTVI > –0.47	1.99 (1.02 to 3.88)	0.044	0.81 (0.39 to 1.70)	0.586
PRD ≥ 5.75 deg^2	4.50 (2.33 to 8.69)	< 0.001	2.99 (1.45 to 6.17)	0.003

[A]The GRACE score combines several clinical risk factors, including patient age, history of previous MI and congestive heart failure, ST-segment deviation, elevated cardiac enzymes, renal impairment, systolic blood pressure and HR upon admission, and percutaneous coronary interventions during the hospital stay. HR, heart rate.

1B and Table 1). Patients in the post-MI cohort were enrolled between May 2000 and March 2005 at 2 university centers in Munich, Germany: the German Heart Centre and the Klinikum Rechts der Isar (21, 22). Eligible patients had survived acute MI (<4 weeks), were aged 80 years or more, had sinus rhythm, and did not meet the criteria for secondary prophylactic implantation of ICD before hospital discharge. Patients in the stress-test cohort were included between October 2001 and December 2008 at the Tampere University Hospital (Finnish Cardiovascular Study) (25). Eligible patients were aged 30–80 years, were in sinus rhythm, and underwent a clinically indicated exercise test.

Procedures. We performed EP studies according to the hospital's standard operating procedures. No study-specific invasive procedures were performed on any patient. We did not sedate the patients. All EP studies required placement of a pacing electrode in the right atrium. Atrial pacing was performed at a fixed cycle length (CL), below sinus rhythm CL and slightly above Wenckebach CL. In the atrial-pacing cohort, we compared a 5-minute recording during undisturbed sinus rhythm to a 5-minute recording during fixed atrial stimulation. In the adrenergic-blockade cohort, we compared 5-minute tracings before and after i.v. administration of 0.1 mg/kg metoprolol. Fixed atrial pacing during the entire procedure was used to ensure constant heart rate.

Subjects in the adrenergic-activation cohort were not allowed to eat or drink coffee for 12 hours before the tests. Vigorous exercise and alcohol were forbidden for 48 hours before the tests. All healthy volunteers lay in a supine position in a quiet room for at least 15 minutes before data collection. We used 2 provocations: 2-minute passive head-up tilt-test at 45° and 5-minute low-intensity exercise using a bicycle ergometer. For the latter test, the individual workload was set to achieve a constant heart rate of 110 bpm. For all physiological studies, we used high-resolution (2,048 Hz) digital ECG (TMS; Porti System) recorded in Frank leads configuration throughout the entire procedure.

For the post-MI cohort, we used 30-minute high-resolution (1,600 Hz) digital ECG (TMS; Porti System) recorded in Frank leads configuration. Recordings were performed within the second week after MI in resting conditions in the morning hours and in a supine position. We additionally performed a 24-hour Holter recording (Oxford Excel Holter System, Oxford Instruments; Pathfinder700, Reynolds Medical; and Mortara Holter System, Mortara Instrument) within the second week after MI. For the stress-test cohort, an upright bicycle was used for the exercise test. The workload was increased from 20 to 30 W in a step-wise manner (10 to 30 W/min). For calculation of PRD, a preexercise period of at least 2.5 minutes was recorded using 12-channel digital ECG (500 Hz), which was converted into the Frank leads configuration by means of the inverse Dower matrix (39).

Assessment of PRD. The technique used to calculate PRD is illustrated in Figure 2 and in Supplemental Figures 4–6. The prerequisite for computing *dT*° is an ECG tracing recorded in or converted to the 3 orthogonal axes X, Y, and Z. The time positions of the T-waves were identified using previously published algorithms (40, 41). The end of each T-wave was set as the reference point (amplitude = 0 mV). The first step in calculating the new parameter was to transform the Cartesian coordinates X, Y, and Z (Supplemental Figure 4A) into a time series of polar coordinates defined by 2 angles (elevation and azimuth) and the resultant-force amplitude XYZ (Supplemental Figure 4B). For example, we selected a time point *t*1 (Supplemental Figure 4B) and decomposed the XYZ vector into 2 orthogonal vectors on the *y* axis and the transverse (XZ) plane. The angle between the vector and the *y* axis was termed the elevation (42) (Supplemental Figure 4D), with an angle of 0° defined as the vector pointing to the caudal direction. The angle between the vector on the transverse plane and the *x* axis was termed the azimuth (42).

On the basis of the 3 new time signals of the polar coordinates, we defined the weight-averaged direction of repolarization, which can be

Table 3
Multivariable association of TWA and PRD with all-cause and cardiovascular mortality in 2,965 patients undergoing a clinically indicated exercise test (stress-test cohort)

	Multivariable Cox regression analysis			
Risk variable	**All-cause mortality**		**Cardiovascular mortality**	
	Beta (95% CI)	***P* value**	**Beta (95% CI)**	***P* value**
Age, continuous	0.055 (0.042 to 0.068)	<0.001	0.044 (0.027 to 0.063)	<0.001
Sex (yes, no)	–0.535 (–0.790 to –0.280)	< 0.001	–0.960 (–1.386 to –0.531)	<0.001
Diabetes mellitus (yes, no)	–0.393 (–0.675 to –0.111)	0.006	–0.291 (–0.721 to 0.139)	0.184
Previous MI (yes, no)	0.205 (–0.049 to 0.459)	0.115	0.288 (–0.080 to 0.656)	0.126
Beta blocker (yes, no)	0.350 (0.085 to 0.614)	0.010	0.582 (0.164 to 0.999)	0.006
TWA, continuous	0.175 (0.007 to 0.284)	0.002	0.274 (0.133 to 0.414)	<0.001
PRD, continuous	0.198 (0.103 to 0.292)	< 0.001	0.269 (0.136 to 0.401)	< 0.001
TWA × PRD	–0.091 (–0.160 to –0.022)	0.010	–0.136 (–0.244 to –0.048)	0.002

Beta, standardized coefficients.

described by a set of 2 polar coordinates that we called the weight-averaged azimuth (WAA) and the weight-averaged elevation (WAE). WAA and WAE can be calculated using Equations 1 and 2, respectively. For each time point *t*, the resultant-force amplitude XYZ, represented as *Amp(t)* in Equations 1 and 2, was multiplied by the corresponding values for azimuth and elevation at the same time point. The (*Amp(t)* × *Angle(t)*) products were initially summed for the entire duration of the T-wave and thereafter divided by the sum of all resultant-force amplitudes. The result of each equation represents the "with-the-amplitude weighted" average angle, which is measured by means of the same units (*deg rad*) as the angle in Equations 1 and 2. Using the repolarization wave of Supplemental Figure 4 as a backbone, exemplary WAA and WAE values were calculated as illustrated in Supplemental Figure 5.

$$\frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t \times Azimuth_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad \text{(Equation 1)}$$

$$\frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t \times Elevation_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad \text{(Equation 2)}$$

We used the angle $dT°$ between successive repolarization vectors as an estimate of the instantaneous degree of repolarization instability (Figure 2, A–C). The angle $dT°$ was calculated using the dot product (scalar product) equation (43), which by 2 vectors of the same length *r* can be simplified to Equation 3 as illustrated in Supplemental Figure 6. The $dT°$ signal was linearly interpolated with a sampling rate of 2 Hz and filtered using a low-pass filter to remove artifacts. In order to quantify the periodic components of $dT°$, we employed continuous wavelet transformation (Figure 2D). The continuous wavelet transformation provides wavelet coefficients for each scale at each time point. For each scale, the average wavelet coefficient was computed. Finally, scales were converted to pseudofrequencies using an established algorithm (44). PRD was defined as the average wavelet coefficient in the frequency range of 0.1 Hz or less (Figure 2E).

$$\begin{aligned} dT° = a\cos\,[&\sin(WAE_1) \times \cos(WAA_1) \times \sin(WAE_2) \times \cos(WAA_2) \\ &+ \cos(WAE_1) \times \cos(WAE_2) \\ &+ \sin(WAE_1) \times \sin(WAA_1) \times \sin(WAE_2) \times \sin(WAA_2)] \end{aligned}$$

(Equation 3)

Assessment of TWA. We assessed TWA by the time-domain MMA method according to previously established technologies (26) (GE Healthcare version 5.2). In brief, the MMA algorithm separates odd from even beats. The average morphologies of both the odd and even beats were calculated separately and continuously updated by a weighting factor of 1/8 or 1/32 of the difference between the ongoing average and the new incoming beats. The update was calculated for every incoming beat, resulting in continual moving averages of the odd and even beats. This approach makes the MMA suitable for TWA analysis during the period of activity or during periods of fluctuating heart rates (non–steady state periods) (45). In addition, algorithms were incorporated to reduce the influence of noise and artifacts, such as those caused by pedaling and respiration (46). The TWA values were calculated continuously during the entire exercise test, from rest to recovery, using all precordial leads. Finally, the maximum TWA value at heart rates of less than 125 bpm was derived.

Assessment of other risk predictors. We assessed LVEF by echocardiography or angiography. We obtained short-term and 24-hour HRV in time and frequency domains as previously proposed (47). Since the standard deviation of all normal-to-normal intervals (SDNN) provided the strongest prognostic power of all HRV measures, we used SDNN as a marker of HRV. We assessed QTVI from the resting ECGs according to previously published technological methods (24). We calculated the GRACE score, which combines several clinical risk factors, specifically patient age, history of previous MI and congestive heart failure, ST-segment deviation, elevated cardiac enzymes, renal impairment, systolic blood pressure and heart rate upon admission, and percutaneous coronary interventions during the hospital stay (23).

Animal study. Seven female domestic pigs (60–78 kg) were preanesthetized with propofol (2 mg/kg i.v.) and anesthetized with α-chloralose (150 mg/kg i.v. with supplemental doses of 600 mg in 60 ml saline as required), which has been shown to induce only minimal effects on the cardiac autonomic nervous system (20). Immediately after induction of anesthesia, the trachea was cannulated and the lungs were mechanically ventilated with room air. Constant respiratory frequency and tidal volume were maintained by means of volume-controlled ventilation with a fixed tidal volume (6 ml/kg) and a fixed respiratory rate. In each ani-

mal, the respiratory rate was set individually (respiratory rate 12–18 per minute corresponding to a frequency of 0.20–0.30 Hz) to maintain normal end-tidal CO_2. Respiratory activity was recorded by a piezoelectric thoracic sensor (48). Two hours after the administration of Propofol, a high-resolution 30-minute ECG (2,048 Hz) was recorded in the Frank leads configuration.

Statistics. We present continuous variables as medians with IQRs. Categorical data are presented as proportions. Results are presented as mean values with 95% CI. Results of physiological and EP studies are presented as the ratio of the value after provocation to the corresponding value before provocation with 95% CI. Differences in the logarithmic ratios were assessed by means of a paired Wilcoxon signed-rank test. To evaluate the effects of respiratory activity on PRD, we estimated the square coherence function between respiratory and $dT°$ signals using the cross-spectral method (49). The coherence function (range 0–1) expresses the linear coupling between 2 signals in the frequency domain (50). A square coherence function greater than 0.5 was considered significant (19, 51, 52). The end points of both prognostic studies were all-cause and cardiovascular mortality. We used the standardized definition of cardiovascular death (53, 54). The median follow-up time in the post-MI cohort was 5 years. PRD was dichotomized at the upper quartile of the study population. For dichotomization of other risk markers, we used established cutoff values of 35% or less for LVEF (55), –0.47 or more for QTVI (24), greater than 75 for mean heart rate (56), 70 ms or less for SDNN (56), and 120 or more for the GRACE score (23). We estimated survival curves using the Kaplan-Meier method. Multivariable analyses were implemented by the adaptation of Cox and multinomial logistic regression models. The latter method was used to calculate integrated discrimination improvement (IDI) scores (57). The median follow-up time in the stress-test cohort was 6 years. The prognostic powers of PRD and TWA were tested with univariable and multivariable Cox regression analysis,including age, sex, previous MI, the presence of diabetes mellitus, treatment with beta blockers, and the crossterm between TWA and PRD (TWA × PRD). PRD, TWA, and age were normalized by subtraction of their mean value and division by their SD and were included as scalar factors in the multivariable model. Differences were considered statistically significant when the 2-sided *P* value was less than 0.05. All statistical analyses were performed using CRAN R, version 2.15.1.

Study approval. The ethics committees of Tübingen, Tampere, and Munich approved the studies performed in the physiological, stress-test, and post-MI cohorts, respectively. Written informed consent was obtained from each participant. The animal protocol was in accordance with the German guidelines for use of living animals and was approved by the local governmental commission for animal research (K 5/10, Regierungspraesidium Tübingen, Baden-Wuerttemberg, Germany).

Acknowledgments

K. Rizas was awarded for this work with the ESC 2013 Young Investigator Award in Clinical Science. The study was supported in part by grants from the program "Angewandte klinische Forschung" (AKF) of the University of Tübingen (252-1-0 to A. Bauer). No additional external funding was received for this study. The Autonomic Regulation Trial (post-MI cohort) was supported by Bundesministerium für Bildung, Wissenschaft, Forschung und Technologie (13N/7073/7), the Kommission für Klinische Forschung, and the Deutsche Forschungsgemeinschaft (SFB 386). The Finnish Cardiovascular Study (stress-test cohort) was supported by the Medical Research Fund of Tampere University Hospital (grants 9MO48 and 9N035), the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Emil Aaltonen Foundation, and the Tampere Tuberculosis Foundation. The authors thank the staff of the Department of Clinical Physiology for collecting the exercise test data.

Received for publication October 23, 2013, and accepted in revised form January 16, 2014.

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Periodic Repolarisation Dynamics: A Natural Probe of the Ventricular Response to Sympathetic Activation

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Abstract

Periodic repolarisation dynamics (PRD) refers to low-frequency (≤0.1Hz) modulations of cardiac repolarisation instability. Spontaneous PRD can be assessed non-invasively from 3D high-resolution resting ECGs. Physiological and experimental studies have indicated that PRD correlates with efferent sympathetic nerve activity, which clusters in low-frequency bursts. PRD is increased by physiological provocations that lead to an enhancement of sympathetic activity, whereas it is suppressed by pharmacological β-blockade. Electrophysiological studies revealed that PRD occurs independently from heart rate variability. Increased PRD under resting conditions is a strong predictor of mortality in post-myocardial infarction (post-MI) patients, yielding independent prognostic value from left-ventricular ejection fraction (LVEF), heart rate variability, the Global Registry of Acute Coronary Events score and other established risk markers. The predictive value of PRD is particularly strong in post-MI patients with preserved LVEF (>35 %) in whom it identifies a new high-risk group of patients. The upcoming Implantable Cardiac Monitors in High-Risk Post-Infarction Patients with Cardiac Autonomic Dysfunction and Moderately Reduced Left Ventricular Ejection Fraction (SMART-MI) trial will test prophylactic strategies in high-risk post-MI patients with LVEF 36–50 % identified by PRD and deceleration capacity of heart rate (NCT02594488).

Keywords

myocardial infarction, periodic repolarisation dynamics, risk stratification, spatial dispersion of repolarisation, sudden death, sympathetic nervous system

Disclosure: The authors have no conflicts of interest to declare.
Received: 18 December 2015 **Accepted:** 18 April 2016 **Citation:** *Arrhythmia & Electrophysiology Review* 2016;**5**(1):31–6 **Access at:** www.AERjournal.com
DOI: 10.15420/AER.2015:30:2
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Experimental and clinical studies have demonstrated that enhanced sympathetic autonomic nervous system (SANS) activity can destabilise myocardial repolarisation,[1–4] increasing vulnerability to developing fatal cardiac arrhythmias.[5–8] Accordingly, assessment of SANS activity has always been a major goal for cardiac risk stratification methods. Various non-invasive methods including assessment of heart rate variability (HRV) and baroreflex sensitivity have been employed to study the activity of the SANS under routine clinical conditions.[9] These methods are based on two principles. First, activation of the SANS evokes physiological effects on the cardiovascular system, such as acceleration of heart rate, increased vasomotor tone or systolic contractility.[4] Second, as SANS activity is clustered in low-frequency bursts, SANS-induced physiological responses are likely to exhibit low-frequency dynamics.[10–14]

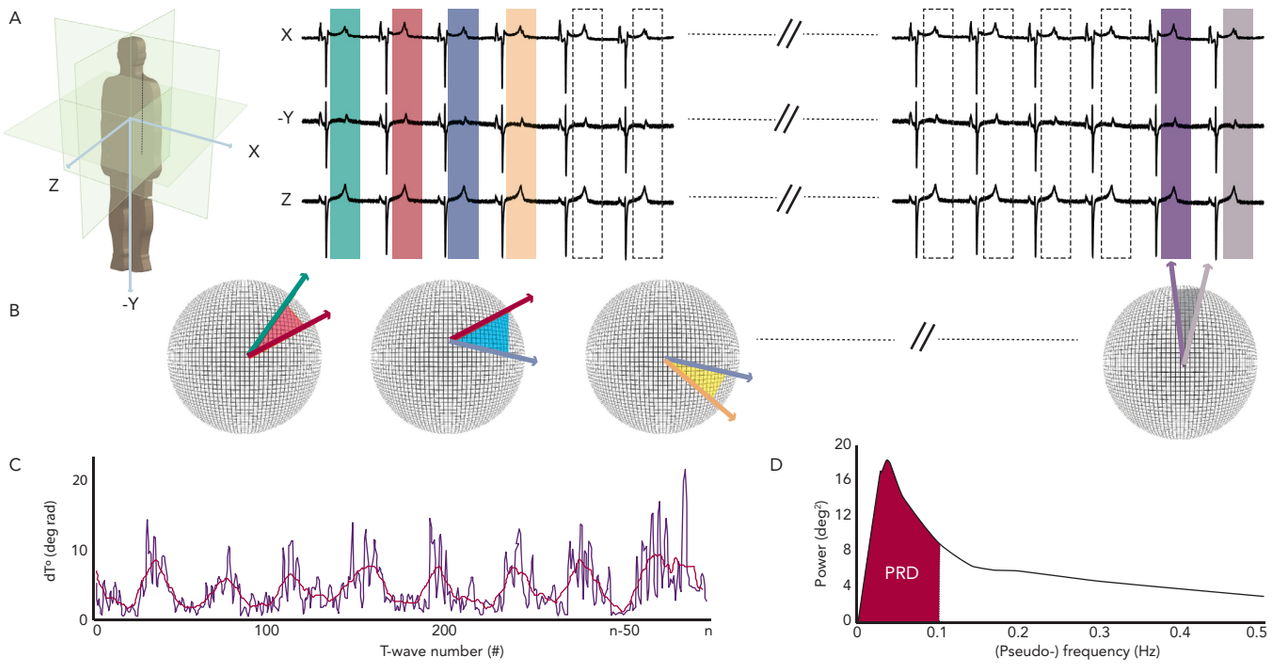
Previous studies have shown that SANS assessment based on HRV and baroreflex sensitivity is a marker of increased vulnerability to fatal cardiac arrhythmias.[15,16] However, both methods are limited by the fact that they only provide an indirect probe of the sympathetic effect on cardiac repolarisation, as they reflect influences on the sinoatrial node and blood vessels and not on the ventricular myocardium. In addition, both HRV and baroreflex sensitivity are confounded by the concomitant action of other systems exhibiting periodic dynamics, such as the parasympathetic nervous system and the renin–angiotensin–aldosterone system, respectively.

We proposed a novel approach to SANS assessment that substantially differs from previous methods.[17] So-called periodic repolarisation dynamics (PRD) evaluates sympathetic activity-associated low-frequency periodic changes of cardiac repolarisation instability and opens new perspectives for identifying high-risk patients, who would potentially benefit from prophylactic interventions. The first section of this review briefly depicts the methodology of PRD assessments. The second section focuses on potential mechanisms of PRD. In the third section, the clinical application of PRD as risk predictor after myocardial infarction (MI) is presented. In the fourth section, we present an alternative method for PRD assessment, which provides some technical advantages over the standard method. The final sections are dedicated to ongoing and future projects aimed at developing individualised treatment strategies.

Methodology of Periodic Repolarisation Dynamics Assessment

PRD is typically assessed using a high-resolution ECG recorded in or converted to the three orthogonal axes X, Y and Z ('Frank lead configuration'). As low-frequency patterns are of interest, the recording

Figure 1. Calculation of Periodic Repolarisation Dynamics



A: Assessment of PRD using a surface ECG recorded in the Frank leads configuration. B: Each T-wave is condensed into a weight-averaged vector of repolarisation (T°). B and C: The angle dT° between two successive repolarisation vectors T° is illustrated in the virtual spheres (B) and is calculated for the entire ECG (C). D: The emerging signal features periodic modulations in the low-frequency range (red line). PRD was quantified by means of wavelet analysis. PRD = periodic repolarisation dynamic.

time should be >10 minutes, although PRD has also been assessed in shorter time periods.[17] Ideally, the ECG is performed under strict standardised conditions in the supine position.

The technique used to calculate PRD is briefly illustrated in *Figure 1*.[17] In a first step, the ECG is converted to a set of polar coordinates defined by two angles (azimuth and elevation) and the 'resultant-force' amplitude (Amp). The beginning and ending of each T-wave are identified using previously published algorithms.[18,19] In a second step, the spatiotemporal characteristics of each T-wave are mathematically integrated into a single vector T° (see *Figure 2*), defined by the so-called weight-averaged azimuth (WAA) and weight-averaged elevation (WAE). The computation of WAA and WAE are given by Equations 1 and 2, respectively:

$$Weight\text{-}averaged\ Azimuth\ (WAA) = \frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t * Azimuth_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad (Equation\ 1)$$

$$Weight\text{-}averaged\ Elevation\ (WAE) = \frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t * Elevation_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad (Equation\ 2)$$

Of note, WAE and WAA are weighted by Amp. This means that each point of the T-wave contributes proportionately to its absolute amplitude to the final direction of vector T°. Accordingly, the boundaries of the T-wave are less crucial than the T-wave peak.

In a third step, the instantaneous degree of repolarisation instability is estimated by the angle dT° between successive repolarisation vectors. dT° can be calculated as the scalar product of two successive repolarisation vectors T°, which by two vectors of the same length r can be simplified by Equation 3 (see *Figure 2*):

$$dT° = a\cos\,[\sin(WAE_1)*\cos(WAA_1)*\sin(WAE_2)*\cos(WAA_2) + \cos(WAE_1)*\cos(WAE_2) + \sin(WAE_1)*\sin(WAA_1)*\sin(WAE_2)*\sin(WAA_2)] \quad (Equation\ 3)$$

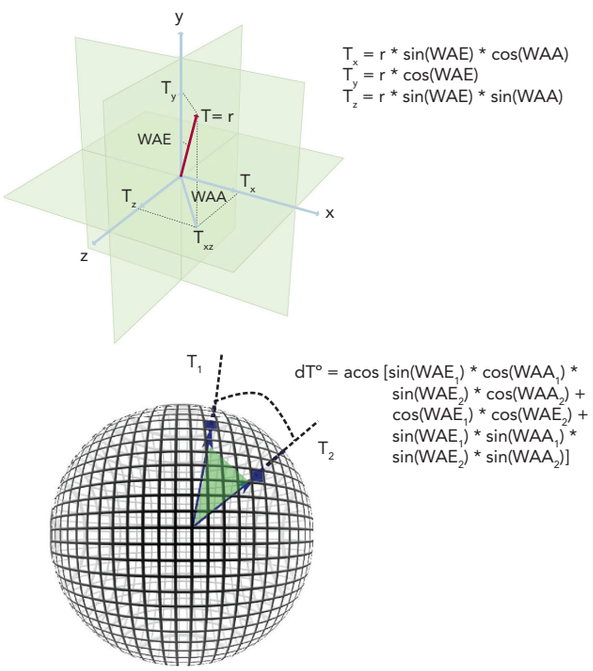
In a final step, low-frequency (≤0.1 Hz) oscillations are quantified within the dT° signal by means of a continuous wavelet transformation (PRDwavelet; see *Figure 1D*).[17]

Potential Mechanisms of Periodic Repolarisation Dynamics

The exact mechanisms underlying PRD are still unknown. However, it is most likely that PRD represents the effect of the sympathetic nervous system on the myocardium.

First, PRD mimics the characteristic low-frequency pattern of efferent sympathetic activity.[11,12,14] Low-frequency patterns can also be found in other biological time series such as heart rate or arterial blood pressure, where they have been shown to correlate with low-frequency sympathetic bursts (muscle sympathetic nervous activity).[10] Moreover, the amplitude of these oscillations has been shown to be related to the level of sympathetic stimulation. For instance, Pagani et al. showed that sympathetic activation provoked by infusion of nitroprusside in healthy human subjects increased low-frequency oscillations of heart rate and systolic arterial blood pressure.[10]

Figure 2: Calculation of the Angle dT° Between Two Successive Repolarisation Vectors T1 and T2



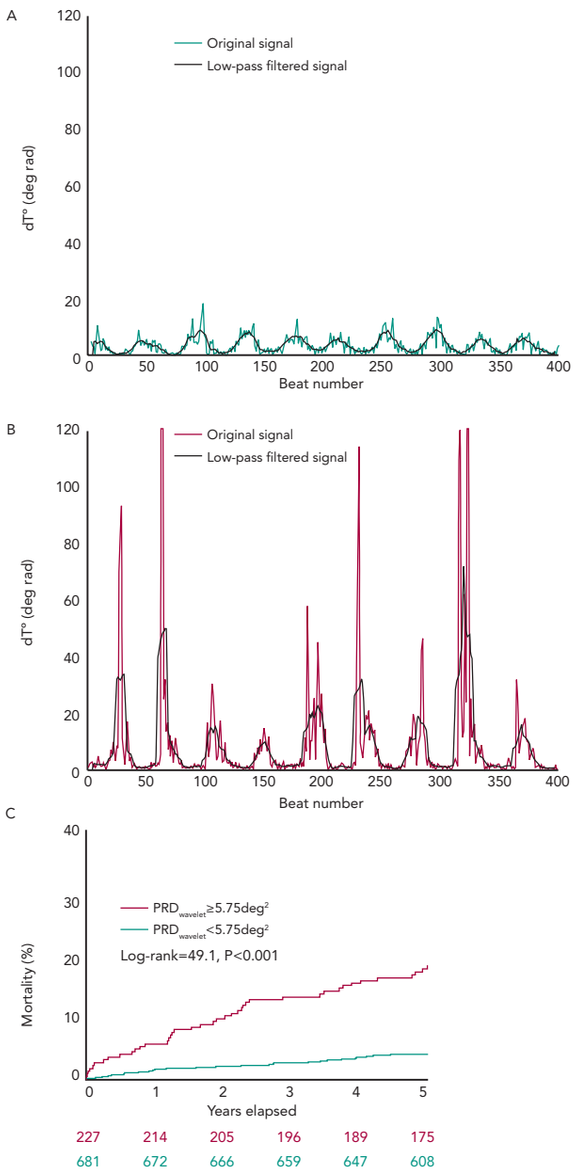
Projection of a vector T on the three orthogonal axes X, Y and Z (upper panel). Two repolarisation vectors T1 and T2 with length r are projected on a virtual sphere (lower panel). The dot product of the two vectors is used to calculate the angle dT° between T1 and T2. WAA = weight-averaged azimuth; WAE = weight-averaged elevation.

Second, indirect evidence comes from physiological and pharmacological studies. Provocations such a tilt test or exercise led to increased PRD in healthy individuals, while pharmacological blockade of the sympathetic nervous system by β-blockers suppressed PRD.[17] PRD remained intact after elimination of HRV and respiratory variability using fixed atrial pacing in patients during an electrophysiological study and fixed-rate, volume-controlled ventilation in a swine model, respectively.[17]

Third, a potential electrophysiological correlate of PRD was identified by Hanson et al.[20] The authors assessed action potential durations (APDs) from unipolar electrograms in patients with heart failure invasively recorded during an electrophysiology study and demonstrated a low-frequency pattern of APD. Although the correlation of oscillations of APD with PRD was not tested in that study, it is likely that both oscillations are driven by the same mechanism.

The mechanistic link of low-frequency sympathetic activity to periodic changes in cardiac repolarisation requires further investigation. A possible mechanism could involve non-uniform response of ventricular myocardial cells to sympathetic activation. Generally, sympathetic activation results in a shortening of APD. Studies conducted over the past few decades demonstrated that the ventricular myocardium is not homogenous, but is comprised of at least three different cell types (epicardial cells, M cells and endocardial cells) with distinct electrophysiological characteristics and pharmacological properties.[21] The electrical heterogeneity between the three cell types of ventricular myocardium creates transmural and apico-basal voltage gradients during the repolarisation phase, causing inscription of the T-wave on the surface ECG.[22] It has been shown that the myocardial cells of

Figure 3: Periodic Repolarisation Dynamics in post-MI Patients



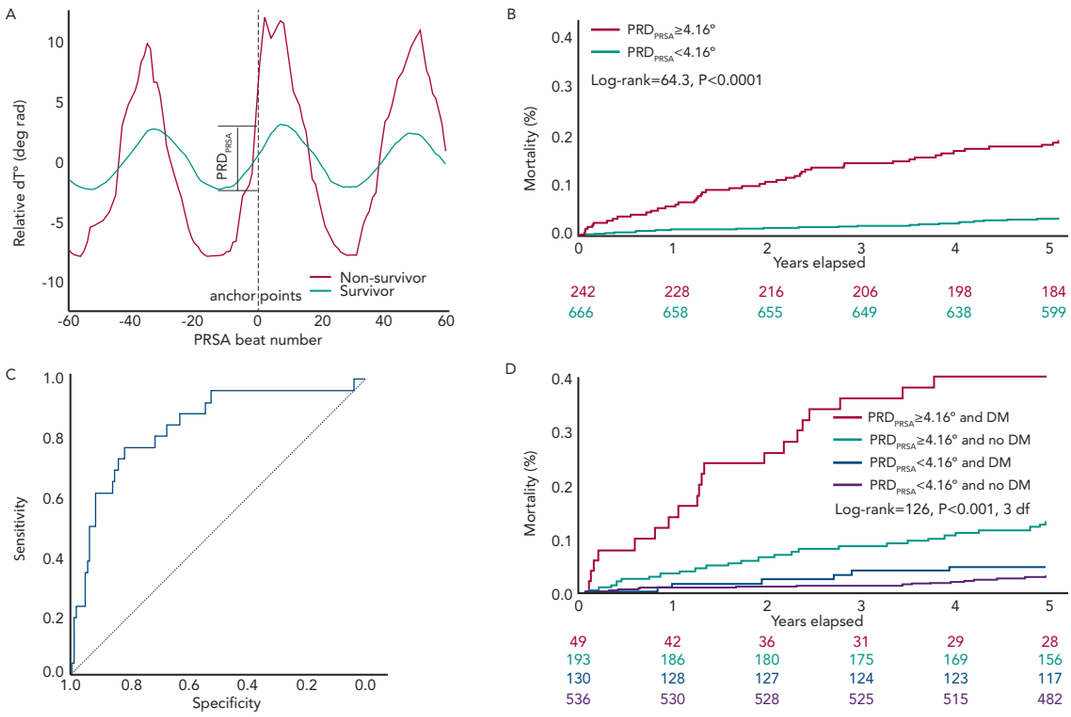
Typical dT° signals obtained from post-MI patients who survived (A, green line) and did not survive (B, red line) the 5-year follow-up period. Both signals show characteristic low-frequency oscillations (black line). However, the amplitude of those oscillations is substantially enhanced in the non-survivor. Cumulative mortality rates of patients stratified by PRD ≥5.75 deg2 (C). PRD = periodic repolarisation dynamic.

the various cell layers respond differently to sympathetic activation. Therefore, theoretically sympathetic activation should lead to changes in the spatio-temporal properties of the T-wave in the surface ECG, which are captured by PRD. The heterogeneity of sympathetically induced APD changes can be augmented in various diseases, including MI,[4] diabetes mellitus[23] and inherited channelopathies.[2,24]

Periodic Repolarisation Dynamics as a Risk Predictor After Myocardial Infarction

The prognostic significance of PRD has been tested in a cohort of 908 survivors of acute MI of the Autonomic Regulation Trial.[17] The primary endpoint was all-cause mortality. In the first 5 years of follow-up, 69 patients died. *Figure 3* shows typical dT° signals in surviving and non-surviving patients. In both signals, low-frequency oscillations of dT°

Figure 4: PRD_{PRSA} as Predictor of Mortality after Myocardial Infarction



A: PRSA transformation of the signals in Figures 3A and 3B. The emerging PRSA signals highlight the periodic components of the dT° signals into a condensed signal consisting of a total of 120 beats around a the central convergence of all anchor points (point 0). The magnitude of the oscillations is quantified by means of PRDPRSA, which is a measure of the amplitude of central part of the PRSA curves. B: Cumulative mortality rates of patients stratified by PRDPRSA ≥4.16 deg2. C: Receiver-operator characteristic curve of PRDPRSA for prediction of 5-year total mortality in the subgroup of patients with DM (n=179). The AUC for this curve was computed to 83.58 %. D: Cumulative mortality rates of patients stratified by PRDPRSA ≥4.16 deg² and presence of DM. AUC = area under the curve; DM = diabetes mellitus; PRD = periodic repolarisation dynamic; PRSA = phase-rectified signal averaging.

were present, but in the non-surviving patient the amplitude of these oscillation was much more pronounced. For survival analyses, $PRD_{wavelet}$ was dichotomised at the upper quartile of the study population.[17] The 5-year mortality rate in the group of the 227 patients with $PRD_{wavelet}$ ≥5.75 deg^2 was 18.2 % compared with 4.1 % in the 681 patients with $PRD_{wavelet}$ <5.75 deg^2 (P<0.001; see *Figure 3B*). In multivariable analyses $PRD_{wavelet}$ was revealed to be a strong predictor of mortality after MI and its predictive ability was independent from established risk predictors, such as left-ventricular ejection fraction (LVEF), the Global Registry of Acute Coronary Events (GRACE) score, presence of diabetes mellitus, reduced HRV and increased QT-variability index.

Alternative Quantification of Periodic Repolarisation Dynamics by Means of Phase-rectified Signal Averaging

The original assessment of PRD from the dT° signal includes continuous wavelet transformation, which requires some computational resources and which might not be available in all software packages. In this section, we therefore describe an alternative method to quantify PRD from the dT° signal using the technique of phase-rectified signal averaging (PRSA). PRSA is a mathematical procedure that allows the extraction of periodicities from complex time series that might include non-stationarities, noise and artefacts.[25] PRSA has been originally used to detect deceleration-related (deceleration capacity; DC) and acceleration-related (acceleration capacity; AC) modulations of heart rate. DC has been shown to yield strong and independent prognostic information in survivors of acute MI.[26] The PRSA technique consists of a three-step procedure and allows for several adjustments, which can optimise the method to the particular signal analysed and the frequency range of the detected oscillations. In the first step, anchor points are selected according to certain properties of the signal. In the case of the dT° signal we defined absolute angle increases greater than 1.25° (deg rad) as anchor points. To amplify the low-frequency periodicities, a low-pass filter of T=9 (average of nine successive beats) is intentionally set up for the selection of anchor points. Although the PRSA technique is able to detect oscillations in a wide frequency range, it has been shown mathematically to be more sensitive for strictly periodic oscillations with frequency {f=1/[2.7*T]}. This means that for frequencies between 0.025 and 0.1 Hz the optimal T ranges between 4 and 15. To maximise the sensitivity at the centre of our spectrum while maintaining a good sensitivity at the boundaries of the frequency range, we used the mean value of T=9. In the second step of the PRSA method, windows (L) around each anchor points are defined to both the left and right of the anchor point (in this case L=60 beats). Finally, in the third step, a new PRSA signal is obtained by averaging over all windows. The central part of the PRSA signal (see *Figure 4A*) is then quantified by Haar wavelet analysis and is defined as PRD_{PRSA}.

Table 1 depicts the Spearman's correlation coefficients between different repolarisation parameters in the 908 patients of the Autonomic Regulation Trial. The correlation coefficient between PRD_{PRSA} and $PRD_{wavelet}$ was 0.854 (95 % CI [0.835–0.871]; P<0.001; see *Table 1*). Of interest, the correlation of PRD_{PRSA} and $PRD_{wavelet}$ with other ECG-based measures of repolarisation was weak (see *Table 1*). *Figure 4A* illustrates the corresponding PRSA transformations of the dT° signals illustrated in *Figure 3*. PRD_{PRSA} was significantly associated with mortality (4.99° [interquartile range (IQR) 3.19] in non-survivors versus 2.58° [IQR 2.29] in survivors; P<0.001). To identify the optimal cut-off value for

Table 1: Spearman's Correlation Coefficient Between Different Repolarisation Parameters

r [95 % CI]	$PRD_{wavelet}$	PRD_{PRSA}	$T_{duration}$	$T_{peak-end}$	T_{AUC}
$PRD_{wavelet}$	1	0.85 [0.83 - 0.87]	0.21 [0.14 - 0.27]	0.27 [0.21 - 0.33]	-0.33 [-0.28 - -0.39]
PRD_{PRSA}	0.85 [0.83 - 0.87]	1	0.20 [0.13 - 0.26]	0.24 [0.18 - 0.30]	-0.16 [-0.10 - -0.22]
$T_{duration}$	0.21 [0.14 - 0.27]	0.20 [0.13 - 0.26]	1	0.91 [0.89 - 0.92]	0.16 [0.10 - 0.22]
$T_{peak-end}$	0.27 [0.21 - 0.33]	0.24 [0.18 - 0.30]	0.91 [0.89 - 0.92]	1	0.08 [0.01 - 0.14]
T_{AUC}	–0.33 [-0.28 - -0.39]	–0.16 [-0.10 - -0.22]	0.16 [0.10 - 0.22]	0.08 [0.01 - 0.14]	1

AUC = area under the curve; PRD = periodic repolarisation dynamic; PRSA = phase-rectified signal averaging.

PRD_{PRSA} we used log-rank statistics for all possible cut-off values. The maximum log-rank value was achieved with a cut-off value of 4.16. *Figure 4B* shows 5-year cumulative mortality rates stratified according to patients with PRD_{PRSA} ≥4.16° and <4.16°. The 242 patients classified to the high-risk group (PRD_{PRSA} ≥4.16°) had a 5-year mortality rate of 19.1 %, compared with 3.5 % for the 666 patients belonging to the low-risk group (PRD_{PRSA} <4.16°). Multivariable analyses revealed that PRD_{PRSA} was a strong predictor of mortality that was independent from LVEF ≤35 %, the GRACE score, HRV and other established risk markers.

Sympathetic-associated modulations of repolarisation might be of great prognostic value in patients with inhomogeneous innervation of the ventricular myocardium. We therefore tested the predictive power of PRD_{PRSA} in a subgroup of 179 patients suffering from diabetes mellitus. PRD_{PRSA} was significantly associated with all-cause mortality in this subgroup. Receiver operating characteristics analysis revealed an area under the curve (AUC) of 83.58 % (see *Figure 4C*; 95 % CI [73.10–91.00]) for prediction of 5-year mortality. *Figure 4D* depicts risk stratification by PRD_{PRSA} in patients with diabetes (red and blue curves) and those without diabetes (green and black curves). The 49 patients with diabetes with abnormal PRD_{PRSA} values have the worst prognosis with a cumulative 5-year mortality rate of 40.80 %.

New Perspectives in Risk Stratification and Risk Reduction Strategies

Periodic Repolarisation Dynamics in Patients With Inherited Channelopathies

Increased sympathetic activity is associated with unfavourable outcomes not only in post-MI patients, but also in patients with inherited channelopathies such as the long-QT syndrome.[2] Assessment of PRD in this group of patients would be of great clinical interest and might open a new era in the identification of high-risk individuals.

The SMART-MI Study

Future interventional studies are needed to test whether high-risk patients identified by PRD or other markers benefit from prophylactic strategies. Considering the fact that prevention of malignant arrhythmias is one of the main goals, prophylactic implantable cardioverter defibrillator implantation might appear to be the most logical approach. However, it might not be the only one. In the Cardiac Arrhythmias and Risk Stratification After Acute Myocardial Infarction (CARISMA) trial, implantable cardiac monitors (ICMs) were used to ultimately detect arrhythmias in high-risk post-MI patients characterised by LVEF ≤40 %.[27] Predefined arrhythmias including AF as well as relevant brady- and tachyarrhythmias could be recorded with a high prevalence (46 % of the patients). Importantly, most of the detected arrhythmias (86 %) were initially asymptomatic, but predicted increased mortality risk, suggesting a potential window of opportunity for pre-emptive interventions.

The upcoming Implantable Cardiac Monitors in High-Risk Post-Infarction Patients With Cardiac Autonomic Dysfunction and Moderately Reduced Left Ventricular Ejection Fraction (SMART-MI) study will test such an approach (Clinicaltrials.gov ID NCT02594488). Survivors of acute MI and LVEF 36–50 % will undergo autonomic testing for the presence of abnormal PRD[17]or DC.[26] Patients with autonomic abnormalities will be randomised to ICM-based or conventional follow-up. Treatment paths have been developed for different kinds of arrhythmias including diagnostic work-up as well as medical or interventional treatments. The primary endpoint will be the time to detection of predefined relevant brady- and tachyarrhythmic events. The effect on clinical endpoints will be tested secondarily.

Conclusion

Spontaneous cardiac repolarisation instability is subject to rhythmic modulations in the low-frequency range (≤0.1Hz), which can be non-invasively assessed using 3D high-resolution ECGs. PRD most likely reflects the response of the ventricular myocardium to sympathetic activation. Factors that predispose to an inhomogeneous sympathetic innervation such as history of MI or diabetes mellitus are associated with increased PRD. In post-MI patients, increased PRD is a strong and independent predictor of mortality. PRSA-based assessment of PRD is a valuable alternative to the more complex conventional wavelet-based PRD assessment. Future interventional studies are needed to test whether PRD-based risk prediction can be translated into risk reduction. ■

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Periodic Repolarization Dynamics – neue Strategien zur Bekämpfung des plötzlichen Herztods

Konstantinos Rizas, Axel Bauer

Bisher wurden Patienten nach Herzinfarkt als Hochrisikogruppe für plötzlichen Herztod eingestuft, wenn die linksventrikuläre Auswurffraktion weniger als 35 % betrug. Doch auch wenn die Pumpfunktion nur moderat oder gar nicht eingeschränkt ist, kann das Mortalitätsrisiko hoch sein. Lebensbedrohliche Situationen kündigen sich häufig als asymptomatische Arrhythmien an. Eine neue Methode, um das Risiko genauer einzuschätzen, ist die Bestimmung der sogenannten Periodic Repolarization Dynamics. Für seine Untersuchungen erhielt Prof. Dr. Axel Bauer 2015 den Präventionspreis der DGIM.

Der plötzliche Herztod

Häufigste Todesursache | Während der letzten 40 Jahre sind die altersadjustierten Sterberaten aufgrund kardiovaskulärer Ursachen deutlich zurückgegangen. Dennoch bleibt der plötzliche Herztod eine der häufigsten Todesursachen in der westlichen Welt [6].

Man geht davon aus, dass bis zur Hälfte aller kardiovaskulären Todesursachen auf den plötzlichen Herztod zurükzuführen sind.

Meistens handelt es sich dabei um ventrikuläre Tachyarrhythmien. Jedoch spielen auch Bradyarrhythmien wie höhergradige AV-Blockierungen und Asystolien eine wichtige Rolle. In etwa 80 % der Fälle besteht eine strukturelle Herzerkrankung, meist in Form einer koronaren Herzerkrankung. Ein Herzinfarkt erhöht das Risiko, am plötzlichen Herztod zu sterben, um den Faktor 6–10 [6].

Prophylaxe mit Defibrillator | In den letzten Jahrzehnten hat sich der implantierbare Defibrillator (implantable cardioverter defibrillator, ICD) als wirkungsvolles Instrument zur Primärprophylaxe des plötzlichen Herztods etabliert. Studien an Hochrisikopatienten konnten klar belegen, dass eine primärprophylaktische ICD-Implantation die Sterblichkeit um bis zu 30 % senken kann [1, 8].

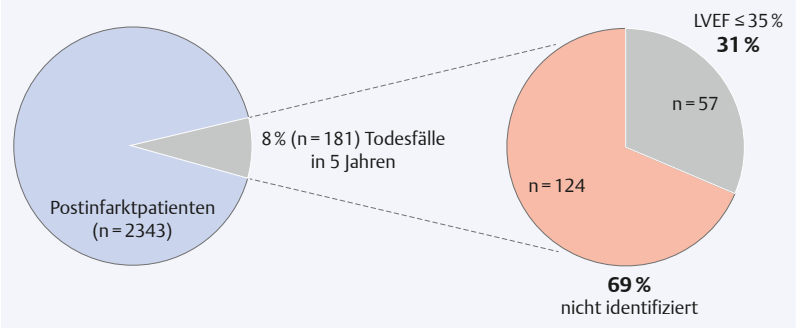

Abb. 1 Dilemma der Risikostratifizierung nach Myokardinfarkt mittels Bestimmung der LVEF: Bei modern therapierten Patienten werden durch das Kriterium einer eingeschränkten LVEF nur weniger als ein Drittel aller Hochrisikopatienten als solche erkannt [2].

Identifikation von Hochrisikopatienten – bisherige Strategien

Auswurffraktion als Kriterium | Trotz hoher absoluter Zahlen ist die Inzidenz des plötzlichen Herztods in der Allgemeinbevölkerung gering. Bisherige Strategien zur Primärprophylaxe zielten daher auf Patientengruppen, in denen eine gewisse Vortestwahrscheinlichkeit für maligne Herzrhythmusstörungen besteht. Patienten, die einen Myokardinfarkt hatten und/oder klinischen Zeichen einer Herzinsuffizienz, sind dabei die beiden Hauptgruppen [1]. In allen Studien zur primärprophylaktischen ICD-Implantation wurden Hochrisikopatienten durch Bestimmung der linksventrikulären Auswurffraktion identifiziert (left ventricular ejection fraction – LVEF). Je nach Studie musste die LVEF 30–35 % oder weniger betragen, damit ein Patient für die ICD-Implantation in Betracht kam [1].

Neue Verfahren notwendig | Wendet man das Kriterium einer eingeschränkten linksventrikulären Funktion jedoch auf modern therapierte Infarktpatienten an, ist es unzureichend. Nur die Minderheit der Patienten, die nach überlebtem Herzinfarkt in den Folgejahren sterben, haben eine LVEF ≤ 35 % [2].

Zwei von drei Todesfällen ereignen sich bei Patienten, deren Pumpfunktion nur moderat oder nicht eingeschränkt ist (▶ **Abb. 1**).

Neue Verfahren, die Hochrisikopatienten nach Myokardinfarkt mit erhaltener oder moderat eingeschränkter Pumpfunktion identifizieren können, sind daher von großer klinischer Bedeutung.

Das kardiale autonome Nervensystem

Schlechte Prognose | Aus klinischen und experimentellen Studien ist bekannt, dass Funktionsstörungen des kardialen autonomen Nervensystems nach Myokardinfarkt eine schlechte Prognose anzeigen [11]. Insbesondere eine erhöhte Sympathikusaktivität bzw. eine Empfindlichkeit myokardialer Zellen auf Sympathikusaktivierung erhöht die Neigung zu malignen Herzrhythmusstörungen [7].

Herzfrequenzvariabilität | Eine Messung der Sympathikuswirkung am Herzen ist jedoch schwierig. Parameter der sog. Herzfrequenzvariabilität (heart rate variability – HRV) analysieren die Modulation der Sinusknoten-Entladungsfrequenz durch die beiden Schenkel des autonomen Nervensystems, den N. sympathicus und den N. vagus. Sie stellen meist ein integrales Maß autonomer Aktivität auf der Ebene des Sinusknotens dar. Rückschlüsse auf die spezifischen Effekte des N. sympathicus auf die Kardiomyozyten des linken Ventrikels sind nicht möglich.

Periodic Repolarization Dynamics

Störung der Repolarisation | Die komplexeste und empfindlichste Phase der elektrischen Herzaktivität ist die Repolarisation. Bereits geringe Instabilitäten können daher fatale Folgen haben.

> Eine erhöhte Sympathikusaktivität am Herzen gilt als ein Schlüsselfaktor zur Destabilisierung der Repolarisation.

Effekte des N. sympathicus auf die kardiale Repolarisation waren jenseits experimenteller Bedingungen nicht messbar.

Niederfrequente Entladungen | Aus direkten Nervenableitungen ist bekannt, dass sympathische Entladungen am Herzen in sog. niederfrequenten „Bursts“ organisiert sind (<0,1 Hz; entsprechend λ>10 s) [5]. Mit Hilfe mathematischer Methoden konnte 2014 erstmalig nachgewiesen werden, dass sich auch niederfrequente Modulationen in der kardialen Repolarisation finden [9]. Dieses elektrokardiografische Phänomen wird „Periodic Repolarization Dynamics“ (PRD) genannt.

Bestimmung per EKG | Um die PRD zu bestimmen, ist eine hochaufgelöste EKG-Aufzeichnung (>1000 Hz) notwendig. Da dieses Phänomen sensibel auf extrinsische wie intrinsische Störfaktoren reagiert, sollte sich der liegende, spontan atmende Patient in einer ruhigen Umgebung befinden. Schematisch erfolgt die PRD-Bestimmung so:

- Die Untersuchung sollte in den orthogonalen Frank-Ableitungen (x, y, z) über einen Zeitraum von mindestens 20 min durchgeführt werden (▶ **Abb. 2A**).
- Vereinfachend wird aus den x-, y- und z-Werten einer jeden T-Welle ein jeweils repräsentativer Vektor bestimmt. Dieser steht für die räumliche und zeitliche Informationen der ventrikulären Repolarisation (▶ **Abb. 2B**).
- In einem 2. Schritt wird jeweils der Winkel dT° zwischen 2 aufeinanderfolgenden T-Wellen-Vektoren berechnet (▶ **Abb. 2B**). Dieser Winkel dient als Maß der momentanen Repolarisationsinstabilität. Meist betragen die Winkeländerungen dT° von T-Welle zu T-Welle nur wenige Grad.
- Trägt man die Winkel jedoch über die Zeit auf, so demaskieren sich periodische dT°-Anstiege etwa alle 15–30 s (▶ **Abb. 2C**).
- Die Ausprägung der niederfrequenten, periodischen dT°-Anstiege kann mittels einer Wavelet-Analyse quantifiziert werden (▶ **Abb. 2D**).

Die PRD-Werte werden als deg^2 angegeben und ergeben sich mathematisch durch Quantifzierung des Wavelet-Spektrums (Fläche unterhalb von 0,1 Hz).

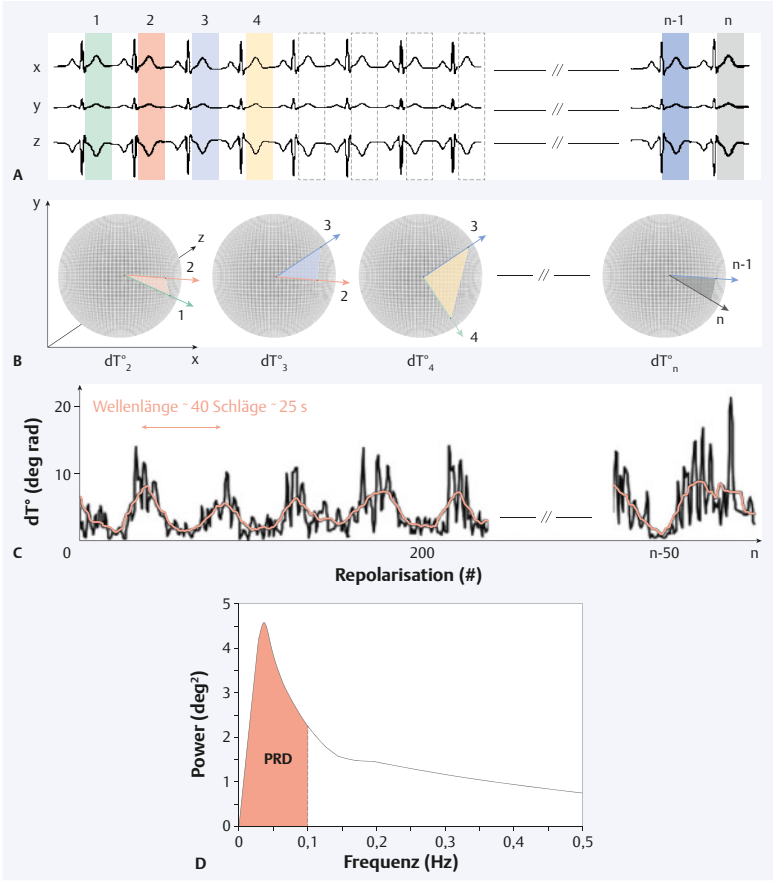

Abb. 2 Schematische Darstellung der Berechnung der „Periodic Repolarization Dynamics“: orthogonale Frank-Ableitungen (A), Winkel zwischen 2 T-Wellen-Vektoren (B), periodische dT°-Anstiege (C), Wavelet-analyse der periodischen dT°-Anstiege (D).

Mechanismen

Ventrikuläre Repolarisation | Die exakten Mechanismen, die PRD zugrunde liegen, sind noch nicht hinreichend erforscht.

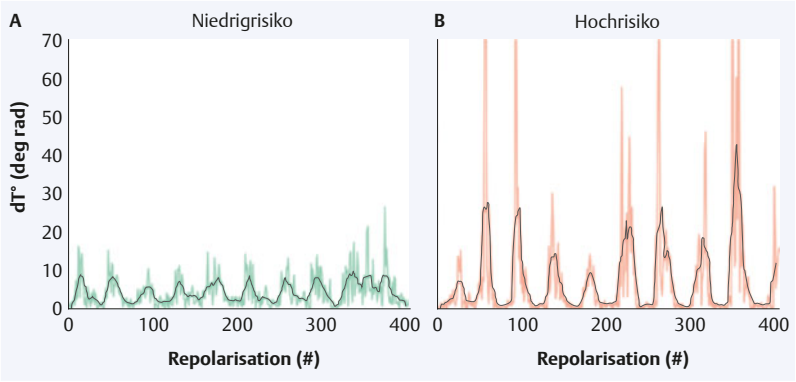

Abb. 3 Typische dT°-Signale bei einem Niedrig- (A) und Hochrisikopatienten (B) nach Myokardinfarkt. Die Amplitude der Modulationen ist bei dem Hochrisikopatienten wesentlich höher [9].

Experimentelle Befunde und theoretische Überlegungen sprechen jedoch dafür, dass PRD die Effekte niederfrequenter sympathischer Entladungen auf die ventrikuläre Repolarisation der Kammermuskulatur widerspiegelt.

Eine physiologische sympathische Aktivierung durch körperliche Belastung oder bei einem Kipptischversuch führen bei Gesunden zu einer deutlichen Zunahme der PRD. Betablocker supprimieren dagegen die PRD. Wie elektrophysiologische Untersuchungen zeigen konnten, ist die PRD zudem unabhängig von der Herzfrequenzvariabilität [9].

Auswirkung sympathischer Aktivierung | Sympathische Stimulation verkürzt bekanntlich die Aktionspotenziale der Kardiomyozyten. Unterschiedlich stark beeinflusst werden dabei die Zellen der einzelnen Schichten des Herzens [10]. So verkürzt sympathische Stimulation die Aktionspotenziale der äußeren Myokardschichten stärker als die der mittleren Myokardschicht. Die T-Welle des Oberflächen-EKGs ist die integrale Repräsentation der Phasen 2 und 3 der Aktionspotenziale aller Kardiomyozyten. Es ist daher davon auszugehen, dass sympathische Aktivierung die T-Welle im EKG verändert – wenn auch nicht mit bloßem Auge sichtbar. Da efferente sympathische Aktivität am Herzen in niederfrequenten Clustern (<0,1 Hz) auftritt [5], sind sympathisch induzierte T-Wellen-Modulationen auch in diesem Frequenzbereich zu erwarten.

Tab. 1 Uni- und multivariable Analyse für die Prädiktion der 5-Jahres-Mortalität in 908 Post-Infarktpatienten der ISAR-Risk Studie[9].

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio	**p**	**Hazard Ratio**	**p**
LVEF ≤ 35 %	3,8 (2,2–6,5)	<0,001	2,1 (1,2–3,7)	0,008
GRACE Score ≥ 120	5,5 (3,2–9,5)	<0,001	3,6 (2,1–6,3)	<0,001
Diabetes mellitus	2,6 (1,6–4,2)	<0,001	2,1 (1,3–3,4)	0,005
mittlere HF > 75 / min	2,0 (1,1–3,6)	0,020	1,1 (0,6–2,2)	0,783
SDNN ≤ 70 s	2,0 (1,2–3,3)	0,007	1,7 (1,0–3,1)	0,072
QTVI > –0,47	2,5 (1,6–4,2)	<0,001	1,1 (0,7–2,0)	0,688
PRD ≥ 5,75 deg²	4,8 (2,9–7,7)	<0,001	3,0 (1,8–5,1)	<0,001

GRACE Score: Global Registry of Acute Coronary Events Score; HF: Herzfrequenz; LVEF: linksventrikuläre Ejektionsfraktion; PRD: Periodic Repolarization Dynamics; SDNN: Standardabweichung aller Normal-zu-Normal Intervalle; QTVI: QT-Variabilitäts-Index

„Autonome Narben“ | Eine besondere Situation findet sich bei Patienten nach Myokardinfarkt oder bei Diabetes mellitus. Bei beiden können sich myokardiale Bereiche finden, deren Zellen zwar vital, jedoch autonom denerviert sind („autonome Narben“). Diese Zellen können nicht auf sympathische Stimulation reagieren, wodurch sich die transmurale Dispersion und dementsprechend die PRD erhöht.

PRD als Risikoprädiktor nach Myokardinfarkt

ISAR-Risk-Studie | Eine gesteigerte ventrikuläre Vulnerabilität gegenüber sympathischen Entladungen gilt als ein Hauptfaktor für die Arrhythmogenese nach Myokardinfarkt. Die prognostische Bedeutung einer erhöhten PRD wurde in der ISAR-Risk-Studie an 908 Post-Infarktpatienten getestet [9]. Einschlusskriterien waren

- ein Herzinfarkt innerhalb der letzten 4 Wochen,
- Sinusrhythmus sowie
- ein Alter von 80 Jahren oder weniger.

Bei allen Patienten wurde unter standardisierten Bedingungen mittels 30-minütiger Ruhe-EKG-Aufzeichnung die PRD gemessen. Sie wurden über einen Beobachtungszeitraum von 5 Jahren nachbeobachtet; primärer Endpunkt war die 5-Jahres-Mortalität.

Erhöhter PRD-Wert zeigt Risiko | Während des Beobachtungszeitraums starben 69 Patienten (7,6 %). ▶ **Abb. 3** zeigt die dT°-Signale

- eines Patienten, der überlebt hat (A), sowie
- eines Patienten, der einige Monate nach Infarkt plötzlich verstorben ist (B).

In den Signalen beider Patienten sind niederfrequente Modulationen sichtbar, die jedoch bei dem verstorbenen Patienten deutlich ausgeprägter sind. Dieser Unterschied bestand hochsignifikant in der gesamten Studienpopulation. So betrug die PRD bei Überlebenden durchschnittlich 2,66 deg² (IQR 3,93), bei Verstorbenen hingegen 6,67 deg² (IQR 8,58) (p<0,0001). Multivariable Analysen zeigten, dass der prädiktive Wert von PRD unabhängig von dem anderer etablierter Risikoparameter wie der LVEF, klinischen Markern oder dem GRACE-Score war (▶ **Tab. 1**). Ein erhöh-

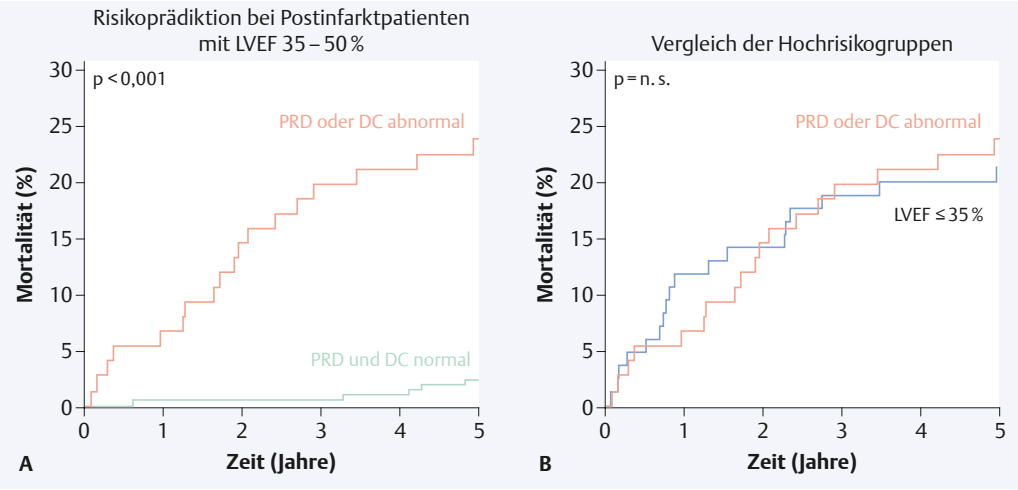

Abb. 4 Risikostratifizierung in 908 Postinfarktpatienten der ISAR-Risk Studie[9]: kumulative Mortalitätskurven bei Post-Infarktpatienten mit LVEF 35–50 % stratifiziert durch die Kombination von PRD und DC (A); kumulative Mortalitätskurven von Postinfarktpatienten mit LVEF ≤ 35 % (blaue Kurve) sowie von Post-Infarktpatienten mit LVEF 35–50 % und abnormaler autonomer Funktion (PRD oder DC abnormal, rote Kurve) (B). DC: Deceleration Capacity; LVEF: linksventrikuläre Ejektionsfraktion; PRD: Periodic Repolarization Dynamics.

ter PRD-Wert zeigte dabei ein ähnlich erhöhtes Risiko wie eine eingeschränkte LVEF (≤ 35 %) an.

Hochrisikopatienten identifizieren

Risiko auch bei LVEF > 35 % | Gegenwärtige Leitlinien betrachten Post-Infarktpatienten mit erhaltener oder nur moderat eingeschränkter LV-Funktion als Niedrigrisikopatienten. Dies ignoriert jedoch die Tatsache, dass sich die Mehrzahl der Todesfälle nach Myokardinfarkt in der Patientengruppe mit LVEF > 35 % ereignet (▶ **Abb. 1**) [2]. Insbesondere auch auf Fälle plötzlichen Herztods trifft dies zu [2].

Risikomarker | Um solche Hochrisikopatienten zu identifizieren, eignen sich Marker der kardialen autonomen Funktion hervorragend. Zielführend ist besonders die Kombination verschiedener Marker, die autonome Funktionsstörungen auf unterschiedlichen anatomischen und funktionellen Ebenen abbilden. ▶ **Abb. 4** zeigt die Effektivität der Risikostratifizierung mittels der Kombination von

- PRD und
- eines weiteren autonomen Markers, der sog. Dezelerationskapazität des Herzens (deceleration capacity, DC) [3].

Die DC lässt sich ebenfalls aus einem Kurzzeit-EKG berechnen und ist ein integrales Maß der vagalen Aktivität auf der Ebene des Sinusknotens.

In der Patientengruppe mit leichtgradig oder moderat eingeschränkter LV-Funktion (LVEF 35–50 %) identifiziert die Kombination aus PRD und DC eine neue Hochrisikogruppe.

Deren Prognose unterscheidet sich nicht von der von Patienten mit eingeschränkter LV-Funktion (LVEF ≤ 35 %). Diese Patientengruppe, die zahlenmäßig der Hochrisikogruppe mit LVEF ≤ 35 % entspricht, bleibt in aktuellen Leitlinien jedoch unberücksichtigt.

Innovative personalisierte Therapieansätze

CARISMA-Studie | Diese Studie erbrachte wesentliche Erkenntnisse bezüglich Art und zeitlichem Auftreten von Arrhythmien bei Hochrisikopatienten nach Myokardinfarkt [4]: Bei 297 Überlebenden eines akuten Herzinfarkts mit LVEF ≤ 40 % wurde ein kardialer Monitor implantiert (implantable cardiac monitor – ICM). Während eines Beobachtungszeitraums von durchschnittlich 1,9 Jahren konnte dieser bei 46 % der Patienten signifikante arrhythmische Ereignisse detektieren. Bemerkenswerterweise waren die meisten Arrhythmien primär asymptomatisch (86 %). Sie zeigten jedoch ein erhöhtes Mortalitätsrisiko an. Insbesondere höhergradige AV-Blockierungen waren ein starker Mortalitätsprädiktor. Bei 28 % der Patienten kam es zum meist asymptomatischem Vorhofflimmern.

Die Ergebnisse der CARISMA-Studie legen demnach nahe: Lebensbedrohliche Ereignisse bei Hochrisikopatienten nach Myokardinfarkt kündigen sich in Form von meist asymptomatischen arrhythmischen Ereignissen an.

Diese rechtzeitig zu erkennen, eröffnet ein Fenster für präventive Maßnahmen.

SMART-MI-Studie | Diese in Kürze startende Studie verfolgt diesen Therapieansatz (Implantable cardiac monitorS in high-risk post-infarction patients with cardiac autonoMic dysfunction And modeRaTely reduced left ventricular ejection fraction; clinicaltrials.gov NCT02594488). Postinfarktpatienten mit LVEF 35–50 % werden auf eine kardiale autonome Dysfunktion getestet. Dabei werden Patienten mit abnormaler PRD

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oder abnormaler DC als Risikopatienten betrachtet. Diese werden 1:1 auf die Implantation eines ICMs mit telemetrischer Überwachung randomisiert. Entdeckt man vordefinierte Arrhythmien, so erfolgt innerhalb von 48 h eine spezifische Intervention – entsprechend definierter Behandlungspfade im Sinn eines multifaktoriellen Ansatzes. Dies kann z. B. eine orale Antikoagulation im Fall von Vorhofflimmern oder eine Ischämiediagnostik im Fall von nichtanhaltenden ventrikulären Tachykardien bedeuten. Bei höhergradigen AV-Blockierungen kann eine Schrittmacherimplantation indiziert sein, bei anhaltenden ventrikulären Tachykardien eine Ablation oder ICD-Implantation.

Konsequenz für Klinik und Praxis

- Der plötzliche Herztod ist eine der häufigsten Todesarten in Deutschland. Die meisten Patienten haben eine erhaltene oder nur moderat reduzierte linksventrikuläre Funktion.
- Periodic Repolarization Dynamics (PRD) beschreibt niederfrequente Modulationen der Repolarisation, die mutmaßlich die Empfindlichkeit des ventrikulären Myokards auf Sympathikusaktivierung widerspiegeln.
- Nach Myokardinfarkt zeigt eine erhöhte PRD ein erhöhtes Mortalitätsrisiko an – unabhängig von anderen Risikofaktoren.
- Die Kombination von Markern der autonomen Dysfunktion erlaubt es, eine neue Hochrisikogruppe von Post-Infarktpatienten mit erhaltener linksventrikulärer Funktion abzugrenzen.
- Eine Biomonitoring-gesteuerte, personalisierte Therapie bei Hochrisikopatienten mit autonomer Dysfunktion könnte ein vielversprechender Ansatz sein.

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Interessenkonflikt
Die Autoren geben an, dass kein Interessenkonflikt besteht.

DOI 10.1055/s-0041-108673
Dtsch Med Wochenschr 2016; 141: 504–508

ISSN 0012-0472

European Heart Journal (2017) **38**, 2110–2118
doi:10.1093/eurheartj/ehx161

Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy

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Received 28 June 2016; revised 9 November 2016; editorial decision 13 March 2017; accepted 14 March 2017; online publish-ahead-of-print 18 April 2017

See page 2119 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx212)

Aims To test the value of Periodic Repolarization Dynamics (PRD), a recently validated electrocardiographic marker of sympathetic activity, as a novel approach to predict sudden cardiac death (SCD) and non-sudden cardiac death (N-SCD) and to improve identification of patients that profit from ICD-implantation.

Methods and results We included 856 post-infarction patients with left-ventricular ejection fraction (LVEF) ≤30% of the MADIT-II trial in sinus rhythm. Of these, 507 and 348 patients were randomized to ICD or conventional treatment. PRD was assessed from multipolar 10-min baseline ECGs. Primary and secondary endpoints were total mortality, SCD and N-SCD. Multivariable analyses included treatment group, QRS-duration, New York Heart Association classification, blood-urea nitrogen, diabetes mellitus, beta-blocker therapy and LVEF. During follow-up of 20.4 months, 119 patients died (53 SCD and 36 N-SCD). On multivariable analyses, increased PRD was a significant predictor of mortality (standardized coefficient 1.37[1.19–1.59]; $P < 0.001$) and SCD (1.40 [1.13–1.75]; $P = 0.003$) but also predicted N-SCD (1.41[1.10–1.81]; $P = 0.006$). While increased PRD predicted SCD in conventionally treated patients (1.61[1.23–2.11]; $P < 0.001$), it was predictive of N-SCD (1.63[1.28–2.09]; $P < 0.001$) and adequate ICD-therapies (1.20[1.03–1.39]; $P = 0.017$) in ICD-treated patients. ICD-treatment substantially reduced mortality in the lowest three PRD-quartiles by 53% ($P = 0.001$). However, there was no effect in the highest PRD-quartile (mortality increase by 29%; $P = 0.412$; $P < 0.001$ for difference) as the reduction of SCD was compensated by an increase of N-SCD.

Conclusion In post-infarction patients with impaired LVEF, PRD is a significant predictor of SCD and N-SCD. Assessment of PRD is a promising tool to identify post-MI patients with reduced LVEF who might benefit from intensified treatment.

Keywords Sudden cardiac death • Implantable cardioverter defibrillator • Risk prediction • Sympathetic nervous system • Electrocardiography

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Introduction

Current guidelines suggest prophylactic implantation of a cardioverter defibrillator (ICD) in post-infarction patients with reduced left-ventricular ejection fraction (LVEF ≤35%).[1,2] This class I recommendation is based, among others, on the results of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II),[3] which randomized high-risk post-infarction patients characterized by reduced LVEF (≤30%) to ICD and non-ICD medical therapy. Although, ICD-treatment was associated with an overall 31%-reduction in the risk of death, 17 ICDs had to be implanted to save one life.[3] One important reason might be that a substantial number of patients in whom sudden cardiac death (SCD) is prevented by ICD-therapy die from non-sudden cardiac death (N-SCD). Indeed, post-hoc analyses of the MADIT-II trial showed that patients who survived an adequate shock for ventricular tachycardia (VT)/ventricular fibrillation (VF) were exposed to a markedly 3.4-fold increased risk of death within 1 year after arrhythmia termination, with a high prevalence of N-SCD.[4] Early identification of these patients might help to initiate pre-emptive strategies for prevention and management of progressive left ventricular dysfunction during long-term follow-up.[4]

Sympathetic activation is an important compensatory mechanism of the failing heart, aiming to restore cardiac output. However, during disease progression sympathetic hyperactivity can become part of the disease, exerting own deleterious effects on the heart.[5] Various studies demonstrated a strong relationship between the level of sympathetic activation and development of adverse cardiac events, including both, arrhythmic but also non-arrhythmic complications. Accordingly, assessment of sympathetic activity in MADIT-II patients might have an important prognostic meaning.

Periodic Repolarization Dynamics (PRD) is a novel electrocardiographic phenomenon that refers to previously unknown oscillations of cardiac repolarization instability.[6] Those oscillations take place in the low frequency range (≤0.1 Hz), occur independently from underlying heart rate variability and can be assessed by means of a multipolar high-resolution resting electrocardiography (ECG). Although the exact mechanisms still need to be identified, electrophysiological and other studies indicated that PRD most likely reflects the effect of phasic sympathetic activation on the myocardial cells.[6] In the Autonomic Regulation Trial (ART), which included 908 survivors of acute MI, increased PRD was a highly significant predictor of 5-year mortality, independently from LVEF and other established risk factors. In that study, however, the vast majority of patients (95%) had LVEF >30%. The prognostic value of PRD in post-MI patients with LVEF ≤30% is currently unknown.

In this work, we therefore tested the prognostic meaning of PRD in MADIT-II patients and hypothesized that increased PRD is a significant predictor of mortality, SCD, and N-SCD. We also hypothesized that PRD might identify patients that need intensified treatment in addition to ICD-therapy. We subsequently validated the prognostic value of PRD in predicting total mortality and cardiac mortality in a contemporary cohort of post-infarction patients with reduced LVEF.

Methods

Study populations

A cohort of 856 patients of the original MADIT-II population[3] were included in the study. The MADIT-II trial included 1232 patients with a previous MI and a LVEF ≤30%. These patients were randomized to receive prophylactic ICD implantation or conventional medical therapy in a 3:2 ratio. Screened patients were excluded if they were in New York Heart Association (NYHA) functional class IV at inclusion; had a MI within the last month; had undergone coronary revascularization within the preceding 3 months; had advanced cerebrovascular or renal disease and suffered from any non-cardiac condition that was associated with a high likelihood of death during the trial. A 12-lead ECG recording was acquired at baseline in supine position using a H12 + Holter device (Mortara Instrument Inc., Milwaukee, WI). This system delivers a high-resolution (1000 Hz), resting continuous ECG recording at baseline for around 10 min. Mason-Likar lead configuration was used. Medication was not changed prior to ECG-recording. Of the 1232 patients 330 patients had to be excluded because no ECG was available. Another 46 patients had to be excluded because of atrial fibrillation (*Figure 1*). The protocol was approved by the ethics committees of each participating centre, and each patient provided written informed consent before inclusion.

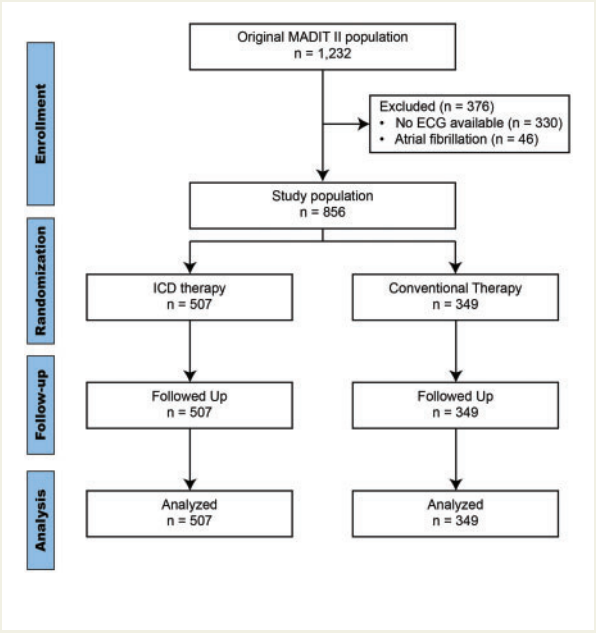

Figure 1 Consort flow-diagram for the MADIT-II population.

The prognostic value of PRD in post-infarction patients with reduced LVEF was prospectively validated in a contemporary cohort of 153 patients who participated in the PRD-MI study (NCT02128477) and were enrolled at the university of Tuebingen between 10/2010 and 2/2014 (details presented in the Supplementary material online).

Assessment of periodic repolarization dynamics

For calculation of PRD Mason-Likar leads were transformed into Frank leads using inverse Dower's transformation. The technical details of PRD assessment have been described elsewhere.[6] Briefly, X-,Y-, and Z-leads are converted to a set of polar coordinates defined by two angles (azimuth and elevation) and the amplitude *Amp*. The beginning and ending of each T-wave are identified using previously published algorithms.[7,8]

In a second step, the spatiotemporal characteristics of each T-wave are mathematically integrated into a single vector T°, defined by the so-called weight-averaged azimuth (WAA) and weight-averaged elevation (WAE):

$$\text{Weight-averaged Azimuth } (WAA) = \frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t * Azimuth_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad \text{(Equation 1)}$$

$$\text{Weight-averaged Elevation } (WAE) = \frac{\sum_{t=T_{start}}^{T_{end}} (Amp_t * Elevation_t)}{\sum_{t=T_{start}}^{T_{end}} Amp_t} \quad \text{(Equation 2)}$$

In a third step, the instantaneous degree of repolarization instability is estimated by the angle dT° between two successive repolarization vectors. dT° can be calculated as the scalar product of two successive repolarization vectors T°, which by two vectors of the same length can be simplified by *Equation 3*.

$$dT^{\circ} = a\cos[\sin(WAE_1) * \cos(WAA_1) * \sin(WAE_2) * \cos(WAA_2) + \cos(WAE_1) * \cos(WAE_2) + \sin(WAE_1) * \sin(WAA_1) * \sin(WAE_2) * \sin(WAA_2)] \quad \text{(Equation 3)}$$

The spectral properties of the dT°-signal are quantified by means of continuous wavelet transformation that provides wavelet coefficients for each scale at each time point. PRD is defined as the average wavelet coefficient corresponding to frequencies of 0.1 Hz or less.[6]

Other risk markers

Following risk markers, that have been previously shown to be associated with outcome in the MADIT-II population[9] were assessed: LVEF (continuous variable), NYHA functional class ≥II, QRS-duration (continuous variable), diabetes mellitus, treatment with beta-blockers at the time of ECG and renal dysfunction defined as blood-urea nitrogen (BUN) level >25 mg/dL. To rule out an interaction with other repolarization markers we compared PRD to Tpeak-to-Tend (TpTe), which was calculated from lead V5 as previously described.[10]

Study endpoints

The primary endpoint of this study was death from any cause. We also tested secondary endpoints including cardiac mortality, SCD, N-SCD, appropriate ICD therapy (A-ICD-Rx), the composite endpoint of SCD and A-ICD-Rx, and the composite endpoint of SCD, N-SCD, A-ICD-Rx, and acute decompensated heart failure (ADHF). All analyses were performed according to the intention-to-treat principle.

Statistical analysis

Continuous variables are presented as means with standard deviations and are compared using the Wilcoxon rank sum test. Categorical data are presented as percentages and are analysed using the χ^2 test. Multivariable analyses were implemented by the adaptation of Cox regression models. PRD was included as continuous marker. All models were adjusted for risk factors as described above. We used concordance statistic (C-index)[11,12] to estimate the general predictive discrimination of the multivariable models. The coefficients of continuous variables are expressed in standardized units (increase per standard deviation [SD]). ICD efficacy was tested in PRD quartiles. Subgroup analyses were performed by means of the regression technique.[13] More specifically, we used interaction terms between ICD-treatment and PRD, as well as therapy with beta-blockers and PRD in order to test the predictive power of PRD in the different subgroups. Internal validation for all endpoints was applied using bootstrapping ($n = 500$).[12,14,15] Correlation between PRD and TpTe was assessed using Pearson's correlation coefficient and was compared against zero. Differences were considered statistically significant when the two-sided *P*-value was <0.05. All statistical analyses were performed using SAS, version 9.4 and CRAN R 3.2.3.

Results

Table 1 shows the demographic and clinical characteristics, as well as treatment and outcome in the studied MADIT-II population. Mean age was 63 ± 11 years. Seventeen percent of the patients were females. Fifty nine percent of the patients were treated with an ICD. Sixty-four percent were treated with beta-blockers. During a mean follow-up time of 20.4 (±12.6) months, 119 patients died. One hundred and one deaths were classified as cardiac deaths. Out of them, 53 were classified as SCD and 36 as N-SCD. Twelve cardiac deaths remained unclassified. One hundred and forty-eight patients were hospitalized for ADHF.

Association of periodic repolarization dynamics with clinical endpoints in the total population

Table 2 shows the statistical association of risk variables with total mortality. Periodic repolarization dynamics was significantly higher in patients who died during the follow-up period than in those who survived ($11.1 \pm 7.7\,\text{deg}^2$ vs. $8.4 \pm 6.2\,\text{deg}^2$, $P < 0.001$). Accordingly, increased PRD was also a significant predictor of mortality in univariable analysis, yielding a HR of 1.38 (standardized coefficient; 95% CI 1.20–1.59; $P < 0.001$). *Figure 2* shows cumulative mortality rates of patients stratified by PRD-quartiles.

Tables 3 and *4* show the association of PRD with different endpoints in multivariable analyses including established risk markers (LVEF, NYHA-classification, renal impairment, QRS-duration, treatment with beta-blockers and presence of diabetes mellitus). Increased PRD was significantly associated with all tested endpoints, including total mortality (1.37 [1.19–1.59]; $P < 0.001$), cardiac mortality (1.39 [1.19–1.63]; $P < 0.001$), SCD (1.40 [1.13–1.75]; $P = 0.003$), N-SCD (1.41 [1.10–1.81]; $P = 0.006$) as well as the combination of SCD, N-SCD, A-ICD-Rx, and ADHF (1.27 [1.15–1.41]; $P < 0.001$).

Table 1 Demographic and clinical characteristics, as well as treatment and outcome in the MADIT-II population ($n = 856$)

Patients' characteristics	
Age ≥65, *n* (%)	394 (46)
Females, *n* (%)	144 (17)
White race, *n* (%)	737 (86)
NYHA classification ≥II	529 (63)
LVEF <25%, *n* (%)	396 (46)
Diabetes mellitus, *n* (%)	298 (35)
Smoking, *n* (%)	690 (81)
Arterial hypertension, *n* (%)	484 (54)
BUN >25 mg/dL, *n* (%)	220 (26)
QRS Duration >120 ms, *n* (%)	245 (29)
Treatment	
ICD, *n* (%)	507 (59)
Beta-blockers, *n* (%)	550 (64)
ACE Inhibitor, *n* (%)	665 (78)
Diuretics, *n* (%)	621 (73)
Amiodarone, *n* (%)	46 (5)
Outcome	
Death, *n* (% 3-year rate)	119 (23)
Cardiac Deaths, *n* (% 3-year rate)	101 (18)
SCD, *n* (% 3-year rate)	53 (9)
N-SCD, *n* (% 3-year rate)	36 (8)
Not-specified, *n* (% 3-year rate)	12 (3)
Non-cardiac deaths, *n* (% 3-year rate)	15 (5)
Unclassified deaths, *n* (% 3-year rate)	3 (1)
VT/VF, *n* (% 3-year rate)	119 (35)
ADHF, *n* (% 3-year rate)	148 (26)
ADHF/Death, *n* (% 3-year rate)	211 (36)

ADHF, acute decompensated heart failure; ACE, angiotensin converting enzyme; BUN, blood urea nitrogen; ICD, implantable cardioverter defibrillator; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

Predictive value of PRD was also independent from that of TpTe (see Supplementary material online, *Table S5*). Addition of PRD improved the predictive power of the multivariable model for prediction of total mortality (increase of C-index from 0.682 [0.628–0.737] to 0.710 [0.656–0.765]), cardiac mortality (increase of C-index from 0.689 [0.632–0.747] to 0.719 [0.661–0.776]), SCD (increase of C-index from 0.652 [0.598–0.706] to 0.685 [0.631–0.740]) and N-SCD (increase of C-index from 0.653 [0.593–0.711] to 0.685 [0.629–0.742]).

The prognostic value of PRD was internally (see Supplementary material online, *Table S7*) and externally validated (see Supplementary material online, *Figure S2 and Table S3*). In the external validation cohort, the prognostic value of PRD in predicting total and cardiac mortality was comparable to that observed in MADIT-II patients. Adding PRD to the risk prediction model improved C-statistics from 0.714 (0.582–0.892) to 0.826 (0.717–0.911) and from 0.807 (0.693–0.904) to 0.889 (0.827–0.942) for prediction of total and cardiac mortality, respectively.

Table 2 Statistical association of risk variables with mortality in the MADIT-II population

Clinical characteristics	Survivors	Non-survivors	*P*-value
N	737	119	
PRD, deg^2 (SD)	8.4 (6.2)	11.1 (7.7)	<0.001
LVEF, % (SD)	23 (5)	22 (6)	0.003
NYHA classification ≥II, *n* (%)	450 (62)	79 (67)	0.301
Diabetes mellitus, *n* (%)	247 (34)	51 (43)	0.049
BUN, mg/dL (SD)	21 (10)	29 (17)	<0.001
Beta-blockers, *n* (%)	496 (67)	54 (45)	<0.001
QRS duration, sec (SD)	0.11 (0.03)	0.13 (0.03)	<0.001

BUN, blood urea nitrogen; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; PRD, periodic repolarization dynamics; SD, standard deviation.

Association of PRD with clinical endpoints in conventionally and ICD-treated patients

The prognostic value of PRD in predicting total mortality was present in both, the 507 patients randomized to ICD-therapy (1.40 [1.17–1.67]; $P < 0.001$) and the 349 patients randomized to conventional therapy (1.34 [1.06–1.69]; $P = 0.014$). Expectedly, the prognostic value of PRD in predicting SCD was present only in conventionally treated patients (1.61 [1.23–2.11], $P < 0.001$). In ICD-treated patients increased PRD did not predict SCD (1.09 [0.71–1.68]; $P = 0.677$) but A-ICD-Rx (1.20 [1.03–1.39]; $P = 0.017$). Confirmatively, in ICD-treated patients increased PRD also predicted the composite of SCD and A-ICD-Rx (1.17 [1.01–1.36]; $P = 0.033$) as well as the composite of all-cause mortality and A-ICD-Rx (1.21 [1.06–1.38]; $P = 0.004$). On the contrary, PRD was only predictive of N-SCD in ICD-treated (1.63 [1.28–2.09]; $P < 0.001$) but not in conventionally treated patients (0.61 [0.28–1.33]; $P = 0.213$).

Effect of beta-blockers

At the time of the ECG-measurement 64% of the MADIT-II patients were treated with beta-blockers. PRD was lower in patients treated with beta-blockers than in those who were not (8.13 ± 5.99 deg^2 vs. 9.82 ± 8.41 deg^2, $P < 0.001$). Nevertheless, there was no significant interaction between PRD and beta-blocker treatment for all tested endpoints (see Supplementary material online, *Table S6*).

Mortality reduction by ICD-treatment according to PRD values

In the study population, ICD-treatment was associated with a 23.7% (95% CI 5.1–53.7%; $P = 0.025$) mortality reduction. As shown in *Figures 3* and *4* ICD-efficacy was strikingly different in the different quartiles of PRD. In the lowest three quartiles, ICD-treatment was

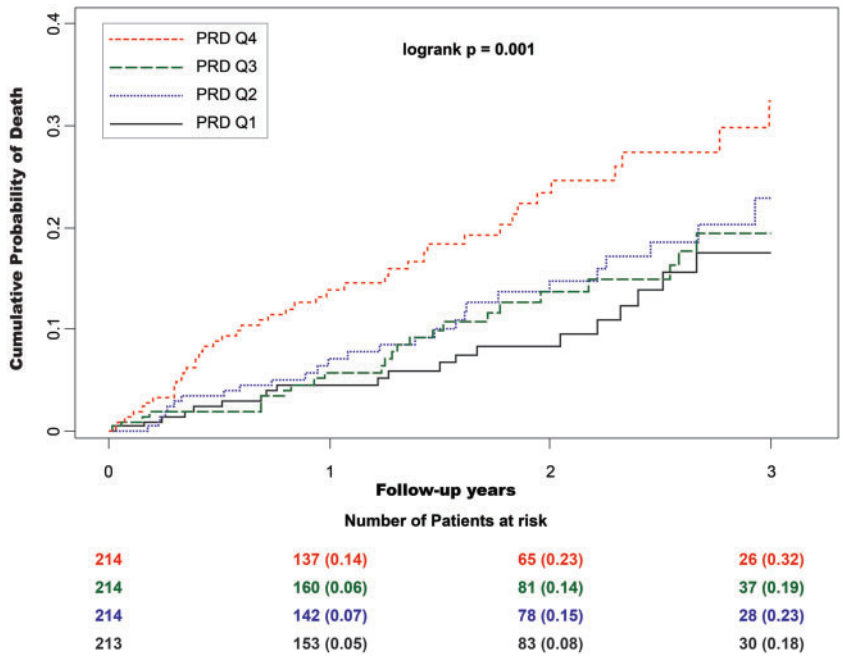

Figure 2 Cumulative 3-year mortality rates in the MADIT-II population. Patients are stratified by PRD quartiles (PRD Q1 ≤4.09 deg^2, PRD Q2 4.10–7.27 deg^2, PRD Q3 7.28–11.51 deg^2, PRD Q4 ≥11.52 deg^2). Because of low number of patients with follow-up time greater than 3 years, Kaplan–Meier curves were right-censored at year 3.

Table 3 Multivariable analyses for prediction of total mortality and cardiac mortality in the MADIT-II population

Risk predictors	Death			Cardiac death		
	HR (95% CI)	X^2	*P*-value	HR (95% CI)	X^2	*P*-value
Tx with ICD	0.66 (0.46–0.95)	5.0	0.026	0.57 (0.38–0.85)	7.7	0.006
PRD (deg^2), per SD	1.37 (1.19–1.59)	17.7	<0.001	1.39 (1.19–1.63)	16.8	<0.001
LVEF (%), per SD	0.91 (0.76–1.09)	1.0	0.313	0.89 (0.73–1.08)	1.4	0.245
NYHA class ≥II	1.08 (0.73–1.60)	0.2	0.694	1.16 (0.76–1.78)	0.5	0.500
Diabetes mellitus	1.17 (0.80–1.72)	0.7	0.407	1.25 (0.83–1.89)	1.2	0.281
BUN >25 mg/dl	2.26 (1.54–3.31)	17.2	<0.001	2.24 (1.48–3.39)	14.4	<0.001
Beta-blockers	0.63 (0.44–0.92)	5.8	0.016	0.62 (0.42–0.93)	5.3	0.022
QRS (s), per SD	1.42 (1.19–1.69)	15.2	<0.001	1.42 (1.17–1.71)	12.8	<0.001

BUN, blood urea nitrogen; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; PRD, periodic repolarization dynamic; Tx, Treatment.

associated with a marked 52.9% (95% CI 25.0–70.4%) mortality reduction ($P = 0.001$;*Figures 3A* and *4*) while in the highest quartile no net effect of ICD-treatment was observed (non-significant mortality increase by 28.7% [95%CI -29.6–135.1%]; $P = 0.412$; $P < 0.001$ for the difference between PRD Q1–Q3 and Q4; *Figures 3B* and *4*). Expectedly, ICD-therapy was associated with a reduction of SCD in all PRD quartiles, which was most pronounced in the lowest three quartiles (71.2% [95% CI 40.7–86.1%] SCD-reduction in multivariable analysis; $P < 0.001$; *Figures 3C* and *4*). In the highest PRD-quartile, a significant SCD-reduction was observed in univariable analysis (*Figure 3D*), which did not reach the level of statistical significance in multivariable analysis (53.1% [95% CI -20.0–81.7%] SCD-reduction; $P = 0.114$; *Figure 4*).

Discussion

Our findings clearly demonstrate that increased PRD is a significant predictor of mortality, SCD and N-SCD in MADIT-II patients. The predictive value of increased PRD was additive to that of established

Table 4 Multivariable analyses for prediction of sudden cardiac death and non-sudden cardiac death in the MADIT-II population

Risk predictors	Sudden cardiac death			Non-sudden cardiac death		
	HR (95% CI)	X^2	*P*-value	HR (95% CI)	X^2	*P*-value
Tx with ICD	0.33 (0.19–0.58)	14.5	<0.001	1.41 (0.68–2.91)	0.9	0.351
PRD (deg^2), per SD	1.40 (1.13–1.75)	9.1	0.003	1.41 (1.10–1.81)	7.4	0.006
LVEF (%), per SD	0.79 (0.61–1.03)	3.0	0.082	1.22 (0.86–1.74)	1.2	0.266
NYHA class ≥II	1.31 (0.72–2.41)	0.8	0.379	1.47 (0.68–3.17)	0.9	0.330
Diabetes mellitus	1.25 (0.71–2.21)	0.6	0.407	1.16 (0.58–2.31)	0.2	0.684
BUN >25 mg/dl	1.71 (0.96–3.06)	3.3	0.070	3.65 (1.79–7.41)	12.8	<0.001
Beta-blockers	0.68 (0.39–1.18)	1.9	0.166	0.63 (0.32–1.25)	1.7	0.189
QRS (s), per SD	1.25 (0.95–1.64)	2.6	0.106	1.61 (1.16–2.22)	8.3	0.004

BUN, blood urea nitrogen; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association; PRD, periodic repolarization dynamic; Tx, Treatment.

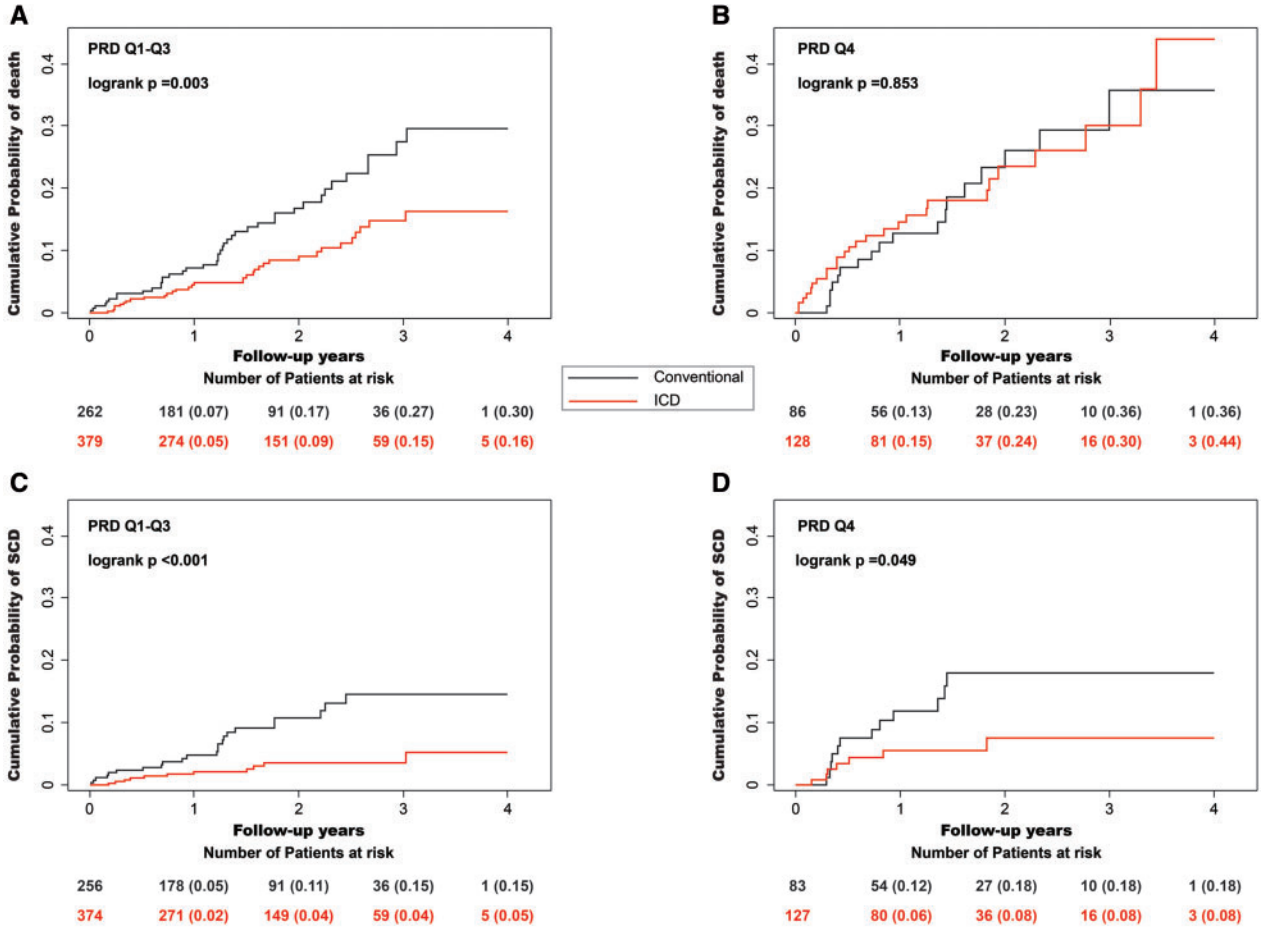

Figure 3 Effect of ICD therapy on mortality- and sudden cardiac death- reduction (SCD) for different levels of periodic repolarization dynamics (PRD). (*A*) In the lowest three quartiles, ICD-treatment was associated with a mortality reduction from 30 to 16% ($P = 0.003$). (*B*) In the highest quartile no significant effect of ICD-treatment was observed ($P = 0.853$). ICD-therapy was associated with a reduction of SCD in all PRD quartiles (*C*) In the lowest three quartiles SCD was reduced from 15 to 5% ($P < 0.001$) and (*D*) in the highest quartile from 18 to 8% ($P = 0.049$).

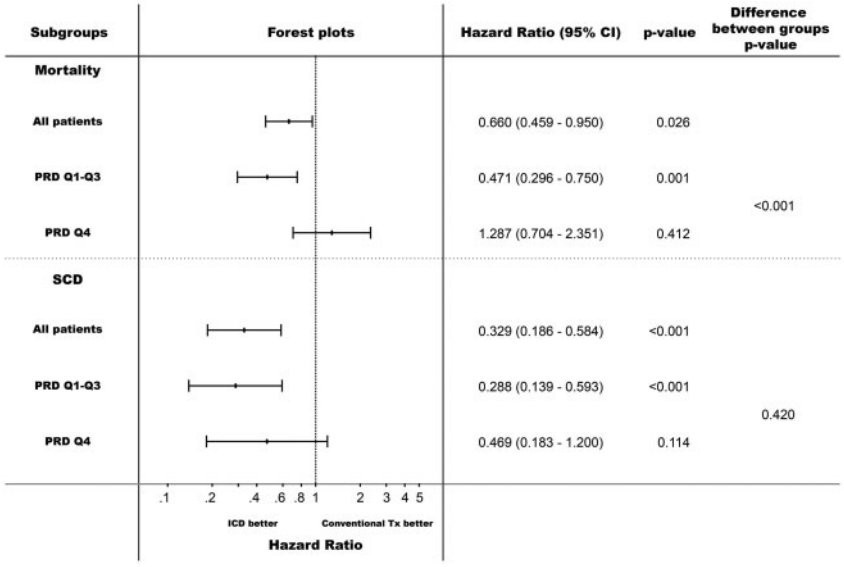

Figure 4 Effect of ICD therapy on mortality- and sudden cardiac death- reduction (SCD) for different levels of periodic repolarization dynamics (PRD). Hazard ratios are calculated from multivariable models adjusted for left-ventricular ejection fraction (cont.), New York Heart Association classification ≥ II, diabetes mellitus, blood urea nitrogen >25 mg/dL, treatment with beta-blockers and QRS-duration.

risk factors that have previously been shown to be associated with outcome in the MADIT-II trial[9] and was present in both, conventionally and ICD-treated patients. While increased PRD was a significant predictor of SCD in conventionally treated patients, it was predictive of N-SCD and adequate ICD-therapy for VT/VF in ICD-treated patients. There was a significant relationship between PRD-level and mortality reduction by ICD-therapy. ICD-therapy substantially reduced mortality by 53.1% in the lowest three PRD-quartiles, while there was no net effect on mortality reduction in the upper quartile, as the observed reduction of SCD was outbalanced by a compensatory increase of N-SCD. The prognostic value of PRD in predicting total and cardiac mortality was externally validated in a contemporary cohort of post-infarction patients with reduced LVEF.

Although the exact mechanisms of PRD need to be identified, previous studies suggested that PRD most likely reflects the dynamic effects of sympathetic activity on the ventricular myocardium.[6] Phasic sympathetic activity predominantly takes place in the low-frequency spectral range[16–20] and exerts different effects on the three cell layers of the ventricular myocardium (epicardial cells, M cells, and endocardial cells).[21,22] Thus, adrenergic activation abbreviates the action potential duration (APD) of epicardial and endocardial cells to a greater degree than the APD of M cells,[23] leading to an increased transmural dispersion of repolarization.[24] Consequently, phasic sympathetic activation induces phasic changes in repolarization localized in the low-frequency spectral range, which might be captured by PRD. This contrasts to static measurements of spatial dispersion of ventricular repolarization such as TpTe, which showed only a very weak correlation with PRD in the present study ($r = -0.12$). Electrophysiological studies in healthy individuals showed that pharmacological blockade of beta-receptors resulted in a striking suppression of PRD, while physiological sympathetic activation by means of physical stress and tilt-testing caused a pronounced augmentation of PRD.[6] Recently, Hanson *et al.* demonstrated oscillatory behaviour of ventricular APD in the same low-frequency range in heart failure patients.[25] Using a modelling study the same group could show that these low-frequency oscillations were enhanced by phasic beta-adrenergic stimulation and phasic mechanical stretch. In the presence of calcium overload and reduced repolarization reserve, both characteristics of heart failure, these oscillations predisposed to early afterdepolarizations and arrhythmic events.[26]

So far, two clinical studies demonstrated a strong link between increased PRD resting levels and adverse events.[6] Periodic repolarization dynamics was evaluated in 908 survivors of acute MI[6,27] enrolled in the ART as well as in 2965 patients of The Finnish Cardiovascular Study (FINCAVAS) who underwent a clinically indicated exercise testing.[6,28,29] In both cohorts, increased level of PRD was highly predictive of total mortality as well as cardiovascular mortality, independently from established risk predictors. However, patients of both cohorts substantially differ from patients of the present study. Both, the ART- and FINCAVAS-studies included low-risk patients with generally preserved LVEF (median 53 and 66%, respectively) without prophylactic ICD-indication. This is in contrast to the current study, which included high-risk patients with severely impaired LVEF in the chronic phase of MI.

In the MADIT-II trial ICD-treatment was associated with an overall 31%-reduction of total mortality. However, previous studies indicated that there is considerable risk heterogeneity within the low-LVEF group, resulting in divergent effects of ICD-therapy on

mortality reduction.[9] Previous studies have shown that a substantial number of patients in whom SCD has been successfully prevented by ICD-therapy subsequently die from non-sudden cardiac causes.[4] Early identification of these patients is crucial for development of pre-emptive strategies against N-SCD. The results of our study show that these patients can be identified by PRD. In the present study, PRD $\geq$11.5 deg^2 (fourth quartile) identified 25% of the patients who had the highest rates of death and SCD. However, although ICD-treated patients with PRD $\geq$11.5 deg^2 also had the highest rates of appropriate ICD-therapies for VT/VF (33.0 vs. 20.6% in the lowest three quartiles; $P = 0.004$), ICD-treatment did not lead to a survival benefit in this group of patients due to an outbalancing increase of N-SCD. Importantly, this group of patients could not be identified by clinical markers, including age, gender, diabetes mellitus, NYHA-class, LVEF, renal function and QRS-duration, which were all evenly distributed (see Supplementary material online, *Table S8*). These findings are in line with pathophysiological considerations. It is well known that sympathetic over-activity predisposes not only to cardiac arrhythmias but also to other unfavourable cardiac conditions, including progression of heart failure and cardiac decompensation.[5,30] In this context, it is noteworthy that PRD was not only predictive of N-SCD but also of ADHF. Patients with PRD in the upper quartile had 67% more ADHF than patients with PRD in the lower three quartiles (see Supplementary material online, *Table S8*).

Our findings have important clinical implications for post-MI management. Thus, PRD might become an important tool to stratify post-MI patients with reduced LVEF into those who already have a substantial benefit from prophylactic ICD-treatment (53.1% mortality reduction by ICD-treatment in patients with PRD <11.5 deg^2) and into those who are at high competing risk of N-SCD and therefore are in need of additional pre-emptive therapies. Such strategies might include optimization of heart failure management, better monitoring and closer follow-up visits. In the studied MADIT-II patients, patients with high PRD levels were less frequently treated with beta-blockers (see Supplementary material online, *Table S8*). Those with high PRD-levels despite beta-blocker therapy might be undertreated. It is well known from epidemiological studies that there is a considerable risk-treatment mismatch in the pharmacotherapy of heart failure, with patients at greatest risk being least likely to receive ACE-inhibitors and beta-blockers at optimal doses.[31] In previous studies, we have shown that beta-blocker treatment can reduce PRD[6]. Therefore, PRD assessment might help to guide individualized beta-blocker therapy.

Our study has several limitations. First, we assessed PRD from 10-min recordings in Mason-Likar configuration, while in the seminal study PRD was assessed from 30-min recordings in Frank-leads configuration. Low-frequency oscillations could be underrepresented in very short-term recordings. Second, patients with atrial fibrillation were excluded from the study, as is presently unknown whether PRD can also be applied to patients with atrial fibrillation. Third, ICD-programming significantly changed over the last decade. We cannot rule out that optimized ICD-programming with longer detection intervals might have led to different findings. Fourth, patients of the MADIT-II trial did not receive medical treatment according to today's standards. Fifth, patients in the original MADIT-II trial were followed up for a relatively short time during the trial (20.4 ± 12.6 months). Sixth, assessment of treatment effects in PRD-quartiles might be limited by small sample size. Seventh, the sample size of the validation cohort was small. Therefore, we were not able to test additional secondary endpoints. Although we also applied internal and external validation techniques to confirm our findings, further prospective studies are needed.

In conclusion, PRD is a significant predictor of mortality and SCD in the MADIT-II trial. Treatment with ICD reduced SCD-rate at all levels of PRD. However, in the highest PRD-quartile, there was no net effect of ICD-therapy on total mortality, as the reduction of SCD was outbalanced by an increase of N-SCD.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

MADIT-II was supported by a research grant from Boston Scientific Corp, St Paul, Minn, to the University of Rochester School of Medicine and Dentistry. The present study was not funded by Boston Scientific Corp. K D Rizas and A Bauer were supported for this work by grants from the EU-CERT-ICD project (Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter Defibrillators in Europe) in terms of travel cost reimbursement. Open Access was funded by the University Hospital of Munich.

Conflict of interest: Dr. Zareba reports grants from Boston Scientific, during the conduction of the MADIT-II study.

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International Journal of Cardiology 249 (2017) 1–5

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Risk prediction in post-infarction patients with moderately reduced left ventricular ejection fraction by combined assessment of the sympathetic and vagal cardiac autonomic nervous system

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ARTICLE INFO

Article history:
Received 7 March 2017
Received in revised form 1 June 2017
Accepted 23 June 2017

Keywords:
Myocardial infarction
Sudden cardiac death
Autonomic dysfunction
Deceleration capacity
Periodic repolarization dynamics
Risk stratification

ABSTRACT

Aim: Most deaths after myocardial infarction (MI) occur in patients with normal or moderately reduced left ventricular ejection fraction (LVEF > 35%). Periodic repolarization dynamics (PRD) and deceleration capacity (DC) are novel ECG-based markers related to sympathetic and vagal cardiac autonomic nervous system activity. Here, we test the combination of PRD and DC to predict risk in post-infarction patients with LVEF > 35%.

Methods and results: We included 823 survivors of acute MI with LVEF > 35%, aged ≤80 years and in sinus rhythm. PRD and DC were obtained from 30-min ECG-recordings within the second week after index infarction and dichotomized at established cut-off values of ≥5.75 deg^2 and ≤2.5 ms, respectively. Patients were classified as having normal (CAF 0), partly abnormal (DC or PRD abnormal; CAF 1) or abnormal cardiac autonomic function (DC and PRD abnormal; CAF 2). Primary endpoint was 5-year all-cause mortality. Within the first 5 years of follow-up, 51 patients died (6.2%). PRD and DC effectively stratified patients into low-risk (CAF 0; n = 562), intermediate-risk (CAF 1; n = 193) and high-risk patients (CAF 2; n = 68) with cumulative 5-year mortality rates of 2.9%, 9.4% and 25.2%, respectively ($p < 0.001$). On multivariable analyses, CAF was independent from established risk factors (GRACE-score, diabetes mellitus, mean heart rate, heart rate variability). Addition of CAF significantly improved the model (increase of C-statistics from 0.732 (0.651–0.812) to 0.777 (0.703–0.850), p = 0.047; continuous NRI (0.400, 95% CI 0.230–0.560, $p < 0.001$); IDI (0.056, 95% CI 0.022–0.122, $p < 0.001$)).

Conclusion: CAF identifies new high-risk post-MI patients with LVEF > 35% which might benefit from prophylactic strategies.

1. Introduction

Survivors of an acute myocardial infarction (MI) face an increased risk for cardiovascular complications including development of malignant arrhythmias, progression of heart failure, myocardial infarction and death [1]. Most preventive strategies such as prophylactic implantation of a cardioverter defibrillator focus on post-infarction patients with reduced left ventricular ejection fraction (LVEF ≤35%). However, most deaths after MI occur in patients in whom left ventricular ejection fraction is not particularly compromised (LVEF > 35%) [1–3]. Accurate identification of high-risk individuals in post-MI patients with LVEF > 35% is of crucial importance to guide prophylactic interventions and reduce mortality. This is currently considered to be an unmet clinical need.

Experimental and clinical studies indicated that important prognostic information can be derived from the functional status of the cardiac autonomic nervous system [4–6]. Sympathetic overactivity and loss of vagal tone have been independently associated with adverse events after myocardial infarction [7–9]. Recently, we identified sympathetic-activity associated low-frequency oscillations of cardiac repolarization which we termed periodic repolarization dynamics (PRD) [10]. Increased PRD has been shown to be associated with poor outcome in patients after myocardial infarction and stable coronary artery disease [10] as well as in patients with severely impaired LVEF [11]. Deceleration capacity (DC) of heart rate quantifies predominantly vagally mediated oscillations of heart rate, with low DC indicating increased risk of adverse events [12]. It is plausible to assume that patients with abnormalities of both branches of the cardiac autonomic nervous system are at highest

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http://dx.doi.org/10.1016/j.ijcard.2017.06.091
0167-5273/

risk. Here, we test the usefulness of a combined risk assessment by means of PRD and DC in post-infarction patients with LVEF >35%.

2. Methods

2.1. Patients

The present study is a post-hoc analysis of the Autonomic Regulation Trial [13]. The study included 823 survivors of acute MI with LVEF >35% in sinus rhythm and aged ≤80 years. Fig. S1 shows the flow chart of patient selection. Patients were enrolled at two university hospitals (German Heart Centre and Klinikum Rechts der Isar, both TU Munich, Germany) between March 2000 and May 2005; last follow-up was performed on May 2010. LVEF was assessed by angiography or biplane echocardiography per Simpson's method within the second week (median 7 days, inter-quartile range (IQR) 5–9 days) after the index MI. The study was approved by the institutional ethical committee.

2.2. Assessment of DC and PRD

PRD and DC were assessed from 30-min high-resolution (1.600 Hz) resting ECGs (TMS; Porti System) according to previously published technologies [10,12]. Recordings were performed within the second week after index infarction in supine position under standardized conditions. The details of both technologies have been described elsewhere [10,12,14]. Fig. S2 shows the scheme of DC and PRD calculation.

Briefly, PRD refers to low frequency modulations of cardiac repolarization instability. To calculate PRD, the spatiotemporal characteristics of each T-wave are mathematically integrated into a single vector $T°$, defining the main direction of the T-wave in space. The instantaneous degree of repolarization instability is estimated by the angle $dT°$ between two successive repolarization vectors. The $dT°$-signal typically exhibits low-frequency (≤0.1 Hz) oscillations that are quantified by means of a continuous wavelet transformation [10].

Computation of DC is based on the transformation of the RR-interval time series by a novel signal processing technology termed Phase-Rectified Signal Averaging (PRSA). RR intervals that are longer than their respective preceding RR interval are identified (so-called anchors). Segments around anchors are averaged to obtain the so-called PRSA-signal. The PRSA-signal can be considered as a condensed version of the original RR-interval time series, including all periodic components of heart rate variability related to decelerations. The central part of the PRSA-signal is quantified by wavelet-analysis to obtain the numerical measure of DC. Thus, DC is an integral measure of all deceleration-related oscillations that take place during the observational period [12]. PRD and DC were dichotomized at established cut-off values, with PRD ≥5.75 deg^2 and DC ≤2.5 ms indicating high risk [10,12].

2.3. Classification of cardiac autonomic function (CAF)

According to PRD and DC patients were classified in three groups of cardiac autonomic function (CAF): normal (CAF 0: PRD <5.75 deg^2 and DC >2.5 ms), partly abnormal (CAF 1: PRD ≥5.75 deg^2 or DC ≤2.5 ms) and abnormal (CAF 2: PRD ≥5.75 deg^2 and DC ≤2.5 ms).

Table 2
Statistical association of risk variables with 5-year mortality.

Risk variable	All patients (n = 823)	Survivors (n = 772)	Non-survivors (n = 51)	p
Age (IQR), years	61 (17)	60 (17)	68 (13)	<0.001
Diabetes, n (%)	157 (19.1)	137 (17.7)	20 (39.2)	<0.001
GRACE score (IQR)	109 (32)	108 (33)	126 (25)	<0.001
LVEF (IQR), %	54 (14)	55 (13)	52 (14)	0.192
DC (IQR), ms	4.9 (4.0)	5.0 (3.9)	2.6 (4.1)	<0.001
PRD (IQR), deg^2	2.66 (3.98)	2.57 (3.73)	5.84 (7,91)	<0.001
CAF 0, n (%)	562 (68.3)	546 (70.1)	16 (31.4)	<0.001
CAF 1, n (%)	193 (23.5)	175 (22.7)	18 (35.3)	0.039
CAF 2, n (%)	68 (8.3)	51 (6.6)	17 (33.3)	<0.001
MHR (IQR), bpm	64 (11)	63 (12)	70 (13)	0.001
SDNN (IQR), ms	93 (39)	94 (39)	81 (39)	<0.001

CAF cardiac autonomic function; DC deceleration capacity; GRACE Global Registry of Acute Coronary Events; IQR inter-quartile range; LVEF left ventricular ejection fraction; MHR mean heart rate; PRD periodic repolarization dynamics; SDNN standard deviation of NN intervals.

2.4. Other risk markers

Mean heart rate (MHR) and standard deviation of all normal-to-normal intervals (SDNN) were calculated according to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [15] and dichotomized at previously established cut-off values of 75 bpm and 70 ms, respectively [10,12,16].

We also estimated the GRACE score proposed for the prediction of long-term prognosis [17]. The GRACE score combines eight factors (age of the patient, heart rate at admission, systolic blood pressure at admission, Killip classification, serum creatinine at admission, ST-segment deviation at admission, cardiac arrest at admission, cardiac biomarker status at admission). The GRACE score's dichotomy was set at 120, optimizing the separation between high- and low-risk cases (log-rank optimization) as no independent guidance for prospective dichotomy is available.

2.5. Statistical analyses

Continuous variables are presented as median and interquartile range, and qualitative data are expressed as percentages. Primary endpoint was 5-year total mortality. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were performed using the Cox proportional-hazards model. The effects of the factors investigated are given as hazard ratios with 95% confidence intervals (CI). Tests in the Cox model and log-rank tests were 2-sided. To test the incremental prognostic value of CAF on top of established risk predictors we implemented C-statistics, integrated discrimination improvement (IDI) score and continuous net reclassification improvement analysis (NRI) [18]. To test for differences between C-statistics, bootstrapping

Table 1
Patients' characteristics.

	All patients	Patients with LVEF ≤35%	Patients with LVEF >35% (study population)				
			All study patients	CAF 0	CAF 1	CAF 2	p
Study characteristics							
Number of patients, n	908	85	823	562	193	68	
Total deaths, n (%)	69 (7.6)	18 (21.2)	51 (6.2)	16 (2.8)	18 (9.3)	17 (25.0)	<0.001
Cardiovascular deaths, n (%)	36 (4.0)	11 (12.9)	25 (3.0)	8 (1.4)	9 (4.7)	8 (11.8)	<0.001
Patients' characteristics							
Median age (IQR), years	61 (17)	64 (16)	61 (17)	58 (17)	65 (16)	68 (10)	<0.001
Females, n (%)	174 (19.2)	13 (15.3)	161 (19.6)	107 (19.0)	41 (21.2)	13 (19.1)	0.798
Diabetes mellitus, n (%)	179 (19.7)	22 (25.9)	157 (19.1)	95 (16.9)	41 (21.2)	21 (30.9)	0.015
Median LVEF (IQR), %	53 (15)	30 (13)	54 (14)	55 (15)	53 (14)	51 (14)	0.001
History of prev. MI, n (%)	84 (9.3)	17 (20.0)	69 (8.4)	40 (7.1)	18 (9.3)	11 (16.2)	0.034
NYHA status							
NYHA I	860 (93.2)	78 (91.8)	782 (95.0)	543 (96.6)	178 (92.2)	61 (89.7)	0.006
NYHA II	31 (3.4)	5 (5.9)	26 (3.2)	13 (2.3)	10 (5.2)	3 (4.4)	0.120
NYHA III	5 (0.6)	0 (0)	5 (0.6)	2 (0.4)	3 (1.6)	0 (0)	0.145
NYHA IV	12 (1.3)	2 (2.4)	10 (1.2)	4 (0.7)	2 (1.0)	4 (5.9)	0.001
Treatment							
PCI, n (%)	848 (93.4)	82 (96.5)	766 (93.1)	534 (95.0)	172 (89.1)	60 (88.2)	0.005
Thrombolysis, n (%)	153 (16.9)	11 (12.9)	142 (17.3)	109 (19.4)	30 (15.5)	3 (4.4)	0.007
CABG, n (%)	17 (1.9)	2 (2.4)	15 (1.8)	7 (1.2)	5 (2.6)	3 (4.4)	0.121
Beta blockers, n (%)	865 (95.3)	85 (100)	780 (94.8)	537 (95.6)	179 (92.7)	64 (94.1)	0.310

CABG, coronary artery bypass graft; CAF, cardiac autonomic function; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3A
Univariable Cox regression analysis of the association of risk markers with 5-year all-cause mortality.

Univariable Cox regression					
Risk variable	HR (95% CI)	p	Risk variable	HR (95% CI)	p
CAF 1 vs. CAF 0	3.4 (1.7–6.7)	<0.001	GRACE score ≥ 120	4.2 (2.4–7.5)	<0.001
CAF 2 vs. CAF 0	9.9 (5.0–19.6)	<0.001	Diabetes	2.9 (1.7–5.1)	<0.001
DC (≤2.5 ms)	4.9 (2.9-8.6)	<0.001	Sex (female)	1.6 (0.9–2.9)	<0.001
PRD (≥5.75 deg^2)	4.1 (2.4–7.1)	<0.001	MHR (>75/min)	2.2 (1.1–4.3)	0.022
LVEF (≤45%)	1.6 (0.8-3.0)	0.171	SDNN (≤70 ms)	2.3 (1.3–4.1)	0.005

was employed based on the creation of pseudo-replicate data sets by random resampling of the data set n times for error estimation (n = 2000 in this study). Differences were considered statistically significant when P < 0.05. Statistical analyses were performed using SPSS (Release 23; SPSS Inc) and CRAN R 3.3.2.

3. Results

The study and patients' characteristics are shown in Table 1. Median age of the 823 patients was 61 years, 161 patients (19.6%) were female. 766 patients (93.1%) were treated with PCI, 780 (94.8%) received beta-blockers. During 5 years of follow-up, 51 patients died (6.2%). 25 of these patients (49%) died due to cardiovascular causes. Among them, 11 (44%) were classified as sudden cardiac death.

Both, PRD and DC were highly significantly associated with 5-year total mortality (Table 2). Thus, PRD was 2.57 deg^2 (IQR 3.73 deg^2) in surviving patients and 5.84 deg^2 (IQR 7.91 deg^2) in non-surviving patients (p < 0.001). DC was 5.0 ms (IQR 3.9 ms) in surviving patients and 2.6 ms (IQR 4.1 ms) in non-surviving patients (p < 0.001).

According to DC and PRD, 562 (68.3%), 193 (23.5%) and 68 (8.3%) patients were classified as low (CAF 0), intermediate (CAF 1) and high (CAF 2) risk patients. Patients with CAF 1 had abnormal PRD in 61.1% of the cases and abnormal DC in 38.9% of the cases.

On univariable Cox regression analysis, presence of CAF 2 was the strongest predictor of mortality, yielding a hazard ratio of 9.9 (95% CI 5.0–19.6; p < 0.0001) (Table 3A). Cumulative 5-year mortality rates of patients with CAF 0, 1 and 2 were 2.9%, 9.4% and 25.2%, respectively (Fig. 1A; p < 0.001). Fig. 1B comparatively shows cumulative 5-year mortality rates of patients with LVEF ≤35% who were enrolled during the same time period but not included in the present study. Of note, the mortality rate of patients with CAF2 and LVEF >35% was not statistically different from that of patients with LVEF ≤35% (25.2% vs. 21.3; p = 0.671).

We used two different models to test the independent contribution of the different risk markers to prediction of 5-year all-cause mortality (Table 3B): Model 1 shows the multivariable Cox regression model including PRD ≥5.75 deg^2 and DC ≤2.5 ms as separate variables. Both, PRD ≥5.75 deg^2 and DC ≤2.5 ms were independently associated with the primary endpoint, yielding hazard ratios of 2.4 (1.4–4.4; p = 0.003) and 2.6 (1.4-4.8; p = 0.002), respectively. Model 2 shows the multivariable Cox regression model using the combination of PRD and DC by means of CAF. CAF2 indicated the highest hazard ratio of 6.4 (3.1-13.2; p < 0.001) of all markers tested.

Adding CAF to the risk model led to a significant increase of C-statistics from 0.732 (0.651–0.812) to 0.777 (0.703–0.850; p = 0.047 for difference), continuous NRI (0.400, 95% CI 0.230–0.560, p < 0.001) and IDI (0.056, 95% CI 0.022–0.122, p < 0.001).

4. Discussion

In the present study, we used the combination of two autonomic risk markers to stratify patients after myocardial infarction with normal or moderately reduced LVEF. The findings of our study indicate that prevalence of CAF 2, reflecting abnormalities in both branches of the cardiac autonomic nervous system, is 8% among survivors of acute MI with LVEF >35% who underwent primary PCI and received up-to-date treatment. Abnormalities in at least one branch of the autonomic nervous systems could be detected in 32% of the cases. Patients with CAF 2 had the worst

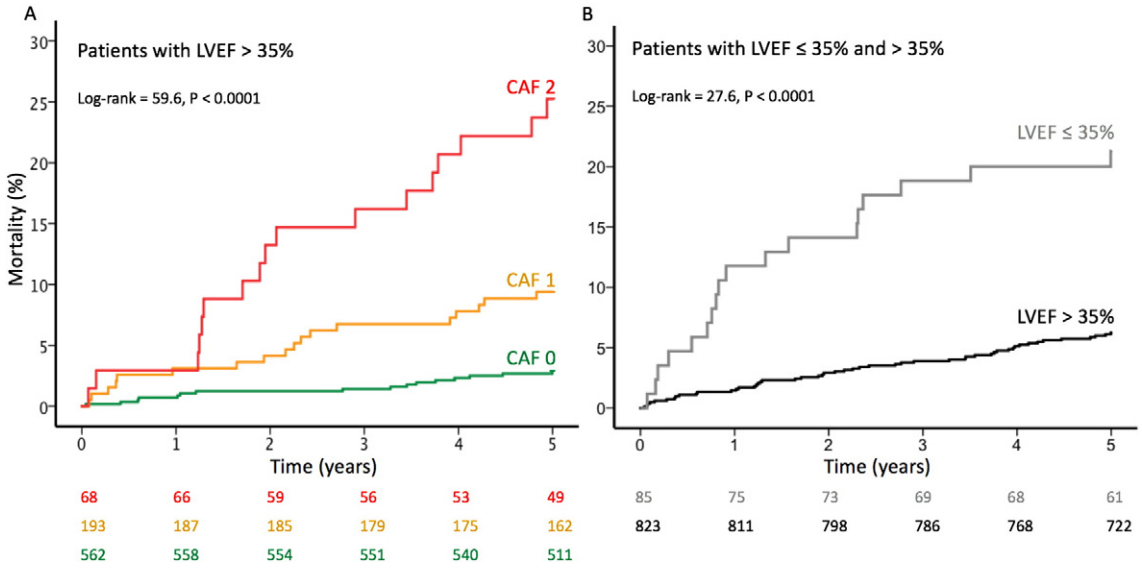

Fig. 1. Risk stratification by CAF and LVEF: Panel A: cumulative mortality curves for patients with LVEF >35% stratified by CAF 0, 1 and 2 (green, yellow and red curves, respectively). Panel B: cumulative mortality curve of all patients with LVEF >35% (actual study population, black curve). For comparison, mortality rate of the 85 excluded patients with LVEF ≤35% is shown (grey curve). CAF, cardiac autonomic function; LVEF, left ventricular ejection fraction.

Table 3B
Multivariable Cox regression analysis of the association of risk markers with 5-year all-cause mortality.

Multivariable Cox regression					
Model 1			Model 2		
Risk variable	HR (95% CI)	p	Risk variable	HR (95% CI)	p
DC (≤2.5 ms)	2.6 (1.4–4.8)	0.002	CAF 1 vs. CAF 0	2.6 (1.3–5.2)	0.006
PRD (≥5.75 deg^2)	2.4 (1.4–4.4)	0.003	CAF 2 vs. CAF 0	6.4 (3.1–13.2)	<0.001
GRACE score ≥ 120	2.5 (1.4–4.7)	0.003	GRACE score ≥ 120	2.5 (1.4–4.7)	0.003
Diabetes	2.1 (1.2–3.9)	0.011	Diabetes	2.2 (1.2–3.9)	0.009
Sex (female)	1.3 (0.7–2.4)	0.471	Sex (female)	1.3 (0.7–2.4)	0.470
MHR (>75/min)	1.2 (0.5–2.6)	0.705	MHR (>75/min)	1.2 (0.5–2.6)	0.704
SDNN (≤70 ms)	2.1 (1.0–4.2)	0.047	SDNN (≤70 ms)	2.0 (1.0–4.1)	0.049

CAF cardiac autonomic function; DC deceleration capacity; GRACE Global Registry of Acute Coronary Events; LVEF left ventricular ejection fraction; MHR mean heart rate; PRD periodic repolarization dynamics; SDNN standard deviation of NN intervals.

prognosis with an estimated 5-year mortality rate of 25.2% which is comparable to that of patients with severely reduced LVEF (≤35%).

Multivariable analyses revealed that both components of CAF, PRD and DC independently contributed to risk prediction. This can be explained by the fact that both, PRD and DC assess complimentary properties of cardiac autonomic function, linked to sympathetic and vagal modulations, respectively. Similar combinations have been proven successful for risk stratification in other diseases such as the long-QT syndrome [19]. While assessment of vagal control of the heart by means of heart rate variability is well established, assessment of sympathetic influences on the ventricles has always remained challenging. The analysis of repolarization variability might, to some degree, provide a solution for this problem. In an elegant study, Porta and colleagues mathematically separated repolarization variability into components related and unrelated to RR-interval and respiration variability [20]. It could be demonstrated that increasing sympathetic activation by gradual tilt testing lead to an augmentation of RR-interval and respiration unrelated repolarization variability. PRD substantially differs from global markers of repolarization variability such as QT-variability index as it specifically captures periodic components of T-vector variability in the low frequency range that occur independently from heart rate variability and respiration [10]. Electrophysiological studies indicated that on the cellular level PRD corresponds to phasic changes of ventricular action potential duration [21]. Although the exact physiological mechanisms of PRD still need to be identified it is most likely that PRD reflects the effect of phasic sympathetic activation on the ventricular myocardium. It has been shown that PRD can be suppressed by beta-blockers while physiological activation of the sympathetic nervous system by exercise or tilt testing augments PRD [10]. Recent studies using computer models integrating ventricular electrophysiology, calcium dynamics, mechanics and beta-adrenergic signaling indicated that additional synergistic mechanisms might be involved in the genesis of PRD [22]. In addition to phasic sympathetic activation PRD is also enhanced by phasic changes of hemodynamic loading, a phenomenon which is known to accompany sympathetic overactivity. Of interest, increased PRD could also be linked to calcium overload and reduced repolarization reserve which are known to be associated with increased risk of adverse events [22].

DC quantifies deceleration-related oscillations of heart rate and is a measure of vagal activity at the level of the sinus node [12]. DC integrates the amplitudes of heart rate oscillations driven by different mechanisms including respiratory activity, baroreflex activity and humoral mechanisms. Thus, DC is an integral measure of autonomic vagal activity and not linked to a specific physiological process [12]. Both markers, PRD and DC, have been shown to be strong predictors of mortality after myocardial infarction in different cohorts [11,12,23], but their combined use has not been studied so far.

The results of our study demonstrate that CAF 2 identifies a new high-risk group among post-infarction patients with LVEF >35% which is comparable with respect to size and prognosis to that of patients with severely reduced LVEF (≤35%). Also, patients with CAF 1 are at a 3.4-fold increased risk of 5-year mortality compared to patients without autonomic abnormalities. These patients are currently not addressed by specific guideline recommendations but might benefit from prophylactic interventions [24]. The ongoing randomized multicenter *Implantable Cardiac Monitors in High-Risk Post-Infarction Patients with Cardiac Autonomic Dysfunction* trial (SMART-MI; NCT02594488) tests a holistic preventive strategy in this high-risk group of patients [25]. High-risk post-infarction patients with LVEF 36-50% and abnormal PRD and/or DC are randomized in a 1:1 fashion to implantation of a cardiac monitor (ICM) including remote monitoring or conventional follow-up. In the experimental group, pre-defined arrhythmias trigger diagnostic and therapeutic treatment paths that might include optimization of medical treatment, revascularization, ablation or device implantation. This concept is based on the results of the CARISMA study which showed that most arrhythmias after MI are asymptomatic but can indicate a substantially increased risk of future adverse events [26].

The limitations of our study need to be recognized. First, the findings of our study are restricted to patients in sinus rhythm and aged ≤80 years. Second, autonomic markers were assessed relatively shortly after index MI. Third, several risk markers including T-wave alternans or baroreflex sensitivity have not been assessed in our study. Forth, primary endpoint was total mortality. Although total mortality is the most robust and unbiased endpoint, the association with arrhythmic mortality might be lost. Finally, findings of our study should be validated by prospective studies.

In conclusion, the combined assessment cardiac autonomic function by means of PRD and DC is a promising approach to identify high-risk individuals after MI with LVEF >35%. Whether risk stratification translates into risk reduction needs to be tested by future interventional studies such as the ongoing SMART-MI trial.

Conflicts of interests

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2017.06.091.

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International Journal of Cardiology 176 (2014) 782–787

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Severe autonomic failure as a predictor of mortality in aortic valve stenosis

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ARTICLE INFO

Article history:
Received 15 November 2013
Received in revised form 14 July 2014
Accepted 26 July 2014
Available online 2 August 2014

Keywords:
Aortic valve stenosis
Cardiac autonomic function
Heart rate turbulence
Deceleration capacity
Risk prediction

ABSTRACT

Background: Identification of new risk markers in aortic valve stenosis (AS) is of great interest. Here, we hypothesized that the presence of severe autonomic failure (SAF) is an important prognostic marker in both, symptomatic patients undergoing invasive treatment for severe AS, and in asymptomatic patients with severe AS who were primarily treated conservatively.
Methods: We prospectively enrolled 300 patients with severe AS (aortic valve area <1.0 cm^2 or mean aortic gradient >40 mm Hg) in sinus rhythm. All patients underwent a 24-h Holter recording for assessment of heart rate turbulence (HRT) and deceleration capacity (DC). Patients with both, abnormal DC and HRT were considered to suffer from SAF.
Results: The first hypothesis was tested in 216 symptomatic patients who underwent successful aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI). During follow-up of 2 years, 29 of these patients died. SAF was the strongest independent predictor of mortality (hazard ratio 5.6, 95% confidence interval 2.6–12.0; $p < 0.001$) with 2-year mortality rates of 50.0% and 10.7% in SAF-positive and SAF-negative patients, respectively ($p < 0.001$). The second hypothesis was tested in 71 patients, who were asymptomatic at study entry and for whom a primarily conservative treatment strategy was proposed. During follow-up, 10 of these patients died. SAF also predicted death in asymptomatic patients with 2-year mortality rates of 52.4% and 8.7% in SAF-positive and SAF-negative patients, respectively ($p = 0.010$).
Conclusions: SAF is a strong and independent predictor of mortality in symptomatic and asymptomatic patients with severe AS.

1. Introduction

Aortic valve stenosis (AS) is the most common type of valvular heart disease in the industrialized world and affects up to 7% of the general population age 65 years and over [1,2]. The natural prognosis of AS varies widely, ranging from rather favorable to deleterious. Therefore, accurate risk assessment is crucial for the selection of the best treatment strategy in the individual patient. According to current guidelines, invasive treatment of severe AS is usually delayed until symptoms occur [3–5]. However, this "wait for symptoms" strategy can be dangerous, as the symptomatic status cannot be reliably assessed in many patients. Hence, novel markers that allow for objective and unbiased estimation of patient risk are of great general interest.

Assessment of cardiac autonomic function provides important insights into the regulatory properties of the cardiovascular system. Markers of cardiac autonomic dysfunction are strong predictors of mortality in post-infarction [6] and heart failure patients [7], yielding independent prognostic information from left ventricular ejection fraction (LVEF) and NYHA class. Alterations of cardiac autonomic function have also been reported in AS [8] but their prognostic meaning is largely unknown.

Here, we hypothesized that cardiac autonomic dysfunction is an important prognostic marker in patients with severe AS. We used a combination of two established Holter-based risk predictors to assess autonomic function. Heart rate turbulence (HRT) [9] quantifies the baroreflex-mediated short-term oscillation of the heart rate following ventricular premature complexes (VPCs). Deceleration capacity (DC) [10] is considered to be representative of tonic vagal activity. Combined abnormalities of HRT and DC have been defined as "severe cardiac autonomic failure" (SAF) [6] and have shown to indicate poor prognosis in post-infarction patients [6]. We tested two different hypotheses: SAF

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http://dx.doi.org/10.1016/j.ijcard.2014.07.088
0167-5273/

predicts mortality in (1) symptomatic patients undergoing invasive treatment for severe AS, as well as in (2) asymptomatic patients with severe AS who were primarily treated conservatively at study entry.

2. Methods

2.1. Recruitment and follow-up

We prospectively studied consecutive patients with severe AS who were referred from September 2009 to November 2012 for evaluation of therapeutic options at a tertiary university center. Patients were included if aortic valve area (AVA) was <1.0 cm^2, mean aortic gradient was >40 mm Hg or jet velocity was >4.0 m/s, confirmed either invasively or by echocardiography. Patients were excluded if they were not in sinus rhythm, if they had an acute coronary syndrome or significant coronary artery stenosis requiring revascularization <4 weeks, if an additional significant valve lesion was present or if the patient's life expectancy was assumed to be less than one year because of non-cardiac diseases.

Therapeutic options for every patient were discussed at a weekly interdisciplinary conference of cardiologists and cardiac surgeons, who were not involved in the study. All recommendations (medical treatment, aortic valve replacement (AVR), transcatheter aortic valve implantation (TAVI)) were based on current guidelines [3–5]. The local ethics committee approved the study. Every patient gave written informed consent.

2.2. Assessment of severe autonomic failure

At enrollment, all patients underwent 24-h Holter recordings (Cardio CM 3000, Getemed, Teltow, Germany) for assessment of HRT and DC. An experienced technician blinded to the patient's clinical status manually reviewed and processed all recordings using standard commercial equipment (CardioDay, Getemed, Teltow, Germany) to obtain the sequence of individual R–R intervals together with beat classification (sinus beat, VPC, artifact).

HRT and DC were calculated according to previously published technologies using established cut-off values by use of customized and validated software [9–11]. Briefly, HRT quantifies the baroreflex-mediated short-term oscillation of the cycle lengths following ventricular premature complexes [9]. The oscillation is composed of an initial acceleration of heart rate followed by a gradual deceleration of heart rate. The two phases of HRT are quantified by two numerical parameters, turbulence onset and turbulence slope. Turbulence onset is calculated as:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100 \ [\%]$$

where RR_{-2} and RR_{-1} are the two RR intervals immediately preceding the VPC coupling interval, and RR_1 and RR_2 are two RR intervals immediately following the compensatory pause [11]. Turbulence slope is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm R–R intervals within the first 15 sinus rhythm RR intervals after the VPC [11]. Hence, in normal subjects, the initial brief acceleration of sinus rate after the VPC is characterized by negative TO, and the subsequent rate deceleration is characterized by positive TS.

DC quantifies the mean amplitude of all deceleration-related oscillations of heart rate observed in the recording period [10]. Assessment of DC is based on a new signal processing algorithm termed phase-rectified signal averaging (PRSA) which is capable of extracting periodic components out of non-stationary, noisy signals [12]. Briefly, the technique consists of five steps. In the first step, RR intervals are identified which are longer than their preceding intervals. In order to exclude artifacts, RR-intervals that are longer than 105% of the preceding RR-interval are excluded. These RR-intervals are called anchors. In the second step, segments around anchors are defined. Please note that segments surrounding adjacent anchors may overlap. In the third and fourth steps, segments are aligned at the anchors and subsequently averaged. The so-called PRSA-signal is quantified by Haar-wavelet analysis [10]:

$$DC = {}^{1}\!/_{4} \times (x_0 + x_1 - x_{-1} - x_{-2})$$

where x_0 and x_1 are the averages of the anchors and the following RR-intervals, while x_{-1} and x_{-2} are the averages of the two RR-intervals preceding the anchors.

In line with previous investigations, patients with combined abnormalities of HRT (turbulence onset ≥0% and turbulence slope ≤2.5 ms/RR interval) and DC (≤4.5 ms) were considered to have SAF [6,13].

2.3. Conventional risk predictors

In all patients, peak and mean aortic gradient, AVA, and LVEF were assessed. In patients who underwent left and right heart catheterization, hemodynamic variables were obtained invasively, as follows: LVEF obtained by the area-length method from a single-plane right anterior oblique projection [14] and AVA calculated using the Gorlin formula [15]. In patients in whom no catheterization was performed, hemodynamic variables were obtained by echocardiography (iE33, Philips Medical Systems). In these patients, LVEF was assessed by the modified Simpson rule with images obtained from apical 4- and 2-chamber views. AVA was estimated by the continuity equation using the velocity–time integral of the aortic and left ventricular outflow tract flows.

The presence of chronic obstructive pulmonary disease (COPD) was defined by long term use of bronchodilators or steroids for lung disease. Extracardiac arteriopathy was considered present if the patient suffered from claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. Neurological dysfunction was defined as a neurological disease severely affecting ambulation or day-to-day functioning. Renal insufficiency was considered present if serum creatinine was >200 μmol/l. Systolic pulmonary artery pressure (PAP_{sys}) was assessed by continuous wave Doppler echocardiography based on tricuspid pressure gradient by adding mean right arterial pressure estimated from inferior vena cava diameter and motion during respiration. The presence of pulmonary hypertension was considered present if PAP_{sys} was >60 mm Hg. Based on these and other risk factors, the logistic EuroSCORE was calculated as previously described [16].

Brain natriuretic peptide (BNP) levels were assessed by immunoassay at study enrollment (ADVIA Centaur® BNP assay, Siemens Healthcare Diagnostics). In 88 patients, N-terminal proBNP (Nt-proBNP) was assessed instead of BNP (Immulite 2000, Siemens Healthcare Diagnostics) because of a change in hospital laboratory standards. In 59 symptomatic and 35 asymptomatic patients, neither BNP nor Nt-proBNP levels were available. BNP and Nt-proBNP were dichotomized at 550 pg/ml [17] and 4691 pg/ml [18], respectively. Patients with BNP ≥550 pg/ml or Nt-proBNP ≥4691 pmol/l were classified as being BNP positive.

2.4. Study endpoints

The primary endpoint was total mortality within the first 2 years of follow-up; the secondary endpoints were cardiac mortality as well as the composite of cardiac mortality and hospitalization resulting from decompensated heart failure within the first 2 years of follow-up. If a patient died during follow-up, the cause of death was verified from hospital and autopsy records and from either the primary physician or those witnessing the death. An independent endpoint committee adjudicated the mode of death. Deaths were categorized as cardiac and non-cardiac. Patients who were asymptomatic at study entry but underwent AVR or TAVI during follow-up were censored at the date of invasive treatment.

2.5. Statistical analysis

Continuous variables are presented as median and IQR and were compared using the Mann–Whitney U test. Qualitative data are expressed as percentages and were analyzed using the chi-square test. The relations of risk variables to the primary and secondary endpoints were investigated with the use of Cox proportional-hazards models. The proportional hazard assumption of the various parameters was investigated by using Schoenfeld residuals. Multivariable Cox regression analysis was adjusted for age and gender. Continuous variables were dichotomized at the median. Mortality rates were estimated by the Kaplan–Meier method. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Differences were considered statistically significant if $p < 0.05$. Statistical analyses were performed using SPSS 20.0.

3. Results

During recruitment period, 678 patients presented for evaluation of AS. 300 patients fulfilled the inclusion criteria. Of these, 229 and 71 patients were classified as being symptomatic and asymptomatic, respectively (Fig. 1).

3.1. Prognostic value of SAF in symptomatic patients undergoing AVR or TAVI

The first hypothesis was tested in 216 of the 300 patients, who were classified as being symptomatic at study entry and who underwent successful AVR (n = 61) or TAVI (n = 155) 16 (median, IQR 3–48) days after enrollment. Patients were aged 79 (73–84) years and 110 (50.5%) were women. AVA was 0.7 (0.5–0.8) cm^2 and LVEF was 55 (45–60) (Table 1). 32 of the 216 patients (14.8%) were SAF-positive. During a median follow-up of 450 (IQR 184–739) days, 29 patients (13.4%) died.

SAF was highly significantly associated with the primary endpoint. The 32 SAF-positive patients had a cumulative 2-year mortality rate of 50.0% compared to 10.7% in the 184 SAF-negative patients ($p < 0.001$; Table 2, Fig. 2A). SAF was also highly significantly associated with the secondary endpoints including cardiac deaths and the composite of cardiac deaths and heart failure-related hospitalizations (Table 2, Fig. 2B). Multivariable analysis revealed that SAF was the strongest predictor of mortality (hazard ratio of 5.6, 95% CI 2.6–12.0; $p < 0.001$) which was independent of elevated serum levels of BNP (hazard ratio of 2.7, 95% CI 1.2–5.9; $p = 0.013$) and other risk factors (Table 3).

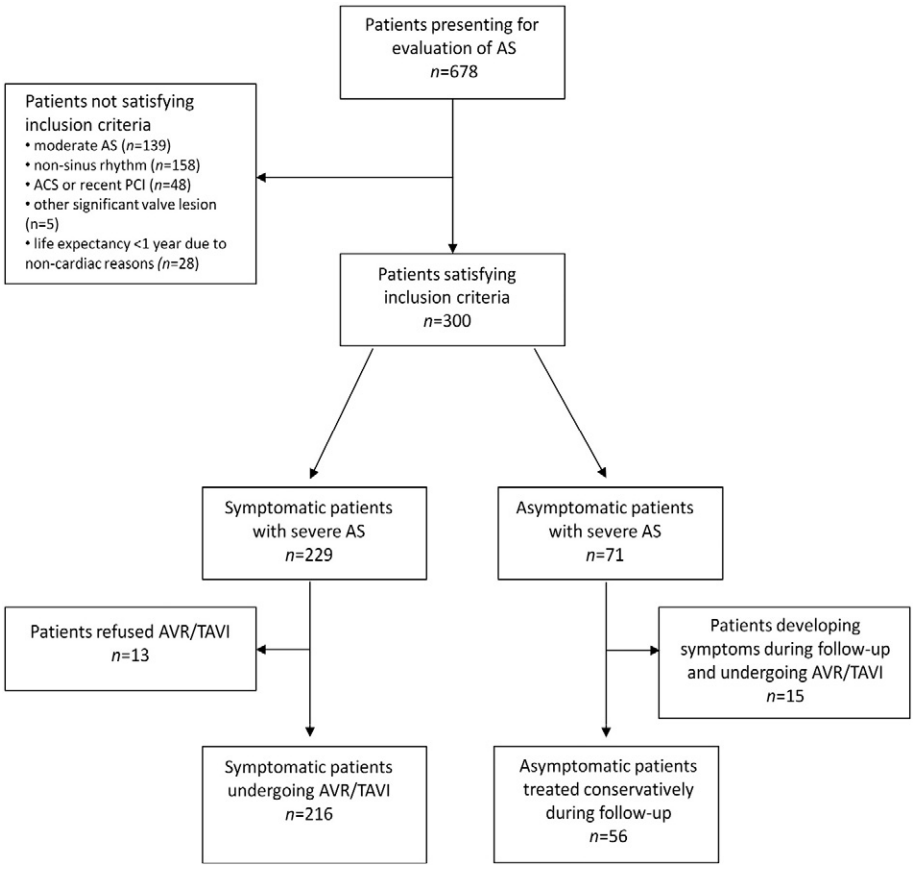

Fig. 1. Flow chart of patient selection.

Table 1
Baseline characteristics of the 216 symptomatic patients, who underwent successful AVR or TAVI.

	All patients (n = 216)	Survivors (n = 187)	Non-survivors (n = 29)	p value
Demographics				
Age (years, IQR)	79 (73–84)	79 (73–83)	82 (75–87)	0.160
Females (%)	109 (50.5%)	90 (48.1%)	19 (65.5%)	0.081
Diabetes mellitus (%)	75 (34.7%)	65 (34.8%)	10 (34.5%)	0.977
Arterial hypertension (%)	169 (78.2%)	146 (78.1%)	23 (79.3%)	0.881
Coronary artery disease (%)	133 (61.6%)	117 (62.6%)	16 (55.2%)	0.446
AVA (cm^2, IQR)	0.7 (0.5–0.8)	0.7 (0.5–0.8)	0.7 (0.6–0.8)	0.811
p mean (mm Hg)	43 (33–52)	43 (33–53)	39 (32–46)	0.176
Risk variables				
COPD (%)	20 (9.3%)	18 (9.6%)	2 (6.9%)	0.637
Extracardiac arteriopathy (%)	22 (10.2%)	19 (10.2%)	3 (10.3%)	0.976
Neurological dysfunction (%)	17 (7.9%)	14 (7.5%)	3 (10.3%)	0.708
Renal insufficiency (%)	69 (31.9%)	54 (28.9%)	15 (51.7%)	0.014
Previous MI (%)	16 (7.4%)	13 (7.0%)	3 (10.3%)	0.457
$PAP_{sys} \geq 60$ mm Hg (%)	14 (6.5%)	11 (5.9%)	3 (10.3%)	0.409
LVEF (%, IQR)	55 (45–60)	55 (45–60)	55 (43–60)	0.504
BNP (pg/ml, IQR)	258 (118–781)	236 (108–617)	815 (237–1389)	0.018
Nt-pro BNP (pg/ml, IQR)	2083 (671–8912)	2406 (694–8971)	838 (412–5401)	0.277
Logistic EuroSCORE (%, IQR)	11.4 (6.3–20.6)	11.3 (5.8–19.8)	14.5 (9.2–36.2)	0.023
SAF	32 (14.8%)	18 (9.6%)	14 (48.3%)	<0.001
Medication				
β-Blockers (%)	158 (73.1%)	139 (74.3%)	19 (65.5%)	0.319
ACEIs/ARBs (%)	177 (81.9%)	154 (82.4%)	23 (79.3%)	0.692
MRAs (%)	87 (40.3%)	72 (38.5%)	15 (51.7%)	0.177
Statins (%)	169 (78.2%)	147 (78.6%)	22 (75.9%)	0.739

ACEI — angiotensin-converting enzyme inhibitor, ARB — angiotensin receptor blocker, AVA — aortic valve area, BNP — brain natriuretic peptide, COPD — chronic obstructive pulmonary disease, IQR — interquartile range, LVEF — left ventricular ejection fraction, MI — myocardial infarction, MRA — mineralocorticoid receptor antagonist, PAP_{sys} — systolic pulmonary artery pressure, and SAF — severe cardiac autonomic failure.

Table 2
Endpoints within 2 years in the 216 symptomatic patients who underwent successful AVR or TAVI.

	All patients (n = 216)	SAF-negative (n = 184)	SAF-positive (n = 32)	p value
Primary endpoint				
All deaths (%)	29 (13.4)	15 (8.2)	14 (43.8)	<0.001
Secondary endpoints				
Cardiac deaths (%)	20 (9.3)	10 (5.4)	10 (31.3)	<0.001
Cardiac deaths & HF-related hospitalizations (%)	37 (17.1)	24 (13.0)	13 (40.6)	<0.001

AVR — aortic valve replacement, HF — heart failure, SAF — severe cardiac autonomic failure, and TAVI — transcatheter aortic valve implantation.

Table 3
Univariable and multivariable regression analyses for prediction of all-cause mortality in the 216 symptomatic patients who underwent successful AVR or TAVI.

Variable	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Logistic EuroSCORE ≥11%	4.5 (1.4–14.8)	0.014	2.8 (0.8–9.8)	0.098
BNP positive	2.1 (1.0–4.5)	0.041	2.7 (1.2–5.9)	0.013
Mean gradient ≥43 mm Hg	0.6 (0.3–1.2)	0.142	0.5 (0.2–1.2)	0.125
AVA ≤0.7 cm^2	1.2 (0.6–2.7)	0.590	1.5 (0.7–3.5)	0.322
SAF	6.4 (3.1–13.2)	<0.001	5.6 (2.6–12.0)	<0.001

AVA — aortic valve area, AVR — aortic valve replacement, BNP — brain natriuretic peptide, CI — confidence interval, SAF — severe cardiac autonomic failure, and TAVI — transcatheter aortic valve implantation. Continuous variables were dichotomized at the median.

13 of the 229 patients (5.7%), who were classified as being symptomatic at study entry, refused invasive treatment.

3.2. Prognostic value of SAF in asymptomatic patients

The second hypothesis was tested in 71 of the 300 patients, who were classified as being asymptomatic at study entry and for whom a primarily conservative treatment strategy was proposed. Patients were aged 74 (68–81) years, 33.8% were women, AVA was 0.9 (0.7–0.9) cm^2 (Table 4). All patients had normal LVEF. Of the 71 patients, 12 (16.9%) were SAF positive. During a median follow-up of 439 (IQR 132–838) days, 15 patients (21.1%) developed symptoms and underwent AVR or TAVI 5.2 ± 4.1 months after enrollment. These patients were censored at the time of interventions. Ten of the 71 patients died before they underwent invasive treatment. SAF also predicted death in the 71 asymptomatic patients (p = 0.010), with estimated 2-year mortality rates of 52.4% and 8.7% in SAF-positive and SAF-negative patients, respectively (Table 5, Fig. 3A). SAF was also highly significantly associated with the secondary endpoints including cardiac deaths and the composite of cardiac deaths and heart failure-related hospitalizations (Fig. 3B).

4. Discussion

Our findings demonstrate that SAF is a novel and powerful predictor of mortality in patients with severe AS. SAF predicted mortality in both symptomatic patients who underwent invasive treatment as well as asymptomatic patients who were primarily treated conservatively. In symptomatic patients, the predictive value of SAF was independent from established risk factors, including the logistic EuroSCORE and BNP.

Risk stratification in AS is an important clinical problem as it is crucial for treatment decision and timing of intervention in patients scheduled for operation. In every individual patient with AS, the patient's natural outcome under a conservative treatment strategy needs to be balanced against the combined risks of intervention and late complications of the prosthesis. Prognosis in asymptomatic patients is assumed to be favorable [19–21], and intervention is thus often delayed until symptoms occur. However, for several reasons, many physicians feel uncomfortable about a “wait for symptoms” strategy [22]. First, dichotomization of patients according to their symptomatic status is problematic because the disease is better described by a continuous spectrum. Concerns arise particularly in patients with mild or nonspecific symptoms, patients who are limited by comorbidities, and elderly patients who are frequently used to adapting their activities to their current

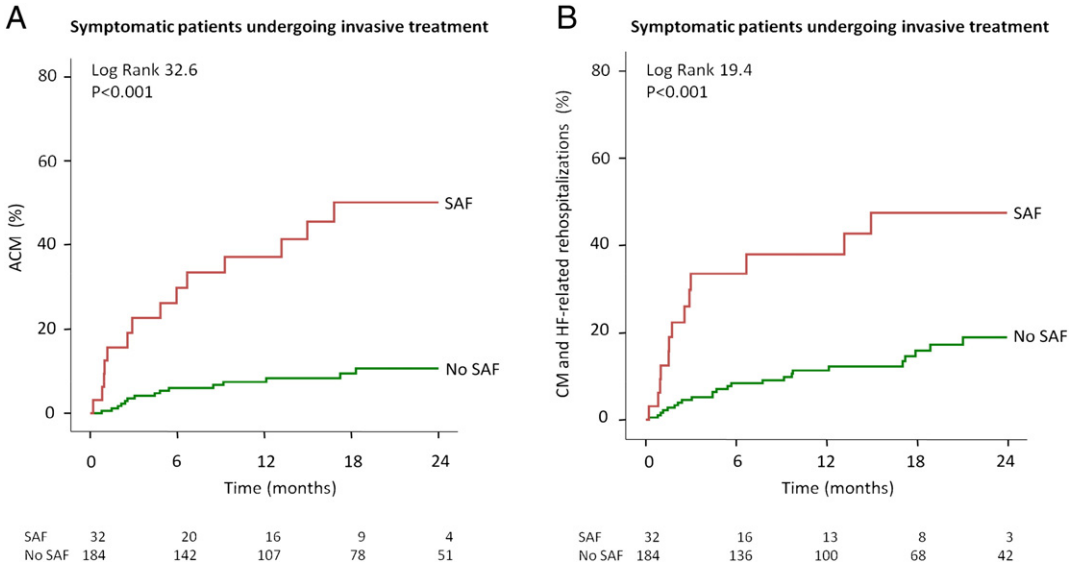

Fig. 2. Cumulative event rates of symptomatic patients with severe aortic stenosis who underwent aortic valve replacement or transcatheter aortic valve implantation stratified by the presence of severe cardiac autonomic failure (SAF). (A) Primary endpoint (all-cause mortality) and (B) secondary endpoint (composite of cardiac mortality and hospitalizations due to decompensated heart failure).

Table 4
Baseline characteristics of the 71 asymptomatic patients.

	All patients (n = 71)	Survivors (n = 61)	Non-survivors (n = 10)	p value
Demographics				
Age (years, IQR)	74 (68–81)	73 (68–80)	75 (71–82)	0.472
Females (%)	24 (33.8%)	22 (36.1%)	2 (20%)	0.477
Diabetes mellitus (%)	21 (29.6%)	16 (26.2%)	5 (50%)	0.148
Arterial hypertension (%)	48 (67.6%)	41 (67.2%)	7 (70%)	0.861
Coronary artery disease (%)	38 (53.5%)	31 (50.8%)	7 (70%)	0.320
AVA (cm^2, IQR)	0.9 (0.7–0.9)	0.9 (0.7–0.9)	0.9 (0.7–1.0)	0.857
p mean (mm Hg)	31 (24–43)	31 (24–43)	34 (16–50)	0.987
Risk variables				
COPD (%)	1 (1.4%)	1 (1.6%)	0 (0%)	0.683
Extracardiac arteriopathy (%)	9 (12.7%)	5 (8.2%)	4 (40%)	0.019
Neurological dysfunction (%)	5 (7.0%)	4 (6.6%)	1 (10%)	0.543
Renal insufficiency (%)	23 (32.4%)	18 (29.5%)	5 (50%)	0.275
Previous MI (%)	17 (23.9%)	12 (19.7%)	5 (50%)	0.052
$PAP_{sys} \geq 60$ mm Hg (%)	1 (1.4%)	0 (0%)	1 (10%)	0.141
LVEF (%, IQR)	55 (50–60)	55 (50–60)	50 (39–55)	0.004
BNP (pg/ml, IQR)	164 (65–424)	123 (54–293)	386 (125–802)	0.097
Nt-pro BNP (pg/ml, IQR)	2086 (356–7714)	2086 (208–11233)	2493 (771–9987)	1.000
Logistic EuroSCORE (%)	7.1 (3.7–14.4)	6.7 (3.6–13.2)	12.9 (5.9–32.2)	0.048
SAF	12 (16.9%)	6 (9.8%)	6 (60%)	0.001
Medication				
β-Blockers (%)	45 (63.4%)	40 (65.0%)	5 (50.0%)	0.343
ACEIs/ARBs (%)	57 (80.3%)	50 (82.0%)	7 (70.0%)	0.378
MRAs (%)	25 (35.2%)	18 (29.5%)	5 (50.0%)	0.199
Statins (%)	52 (73.2)	46 (75.4%)	6 (60.0%)	0.308

ACEI — angiotensin-converting enzyme inhibitor, ARB — angiotensin receptor blocker, AVA — aortic valve area, BNP — brain natriuretic peptide, COPD — chronic obstructive pulmonary disease, IQR — interquartile range, LVEF — left ventricular ejection fraction, MI — myocardial infarction, MRA — mineralocorticoid receptor antagonist, PAP_{sys} — systolic pulmonary artery pressure, and SAF — severe cardiac autonomic failure.

clinical situation. Second, waiting until low-risk patients become high-risk patients can be dangerous because patients often do not immediately present to their physicians at symptom onset. Third, in high-risk patients, peri-operative mortality is increased and long-term outcome might be reduced because of sequelae of longstanding and potentially irreversible left ventricular damage.

The exact mechanisms linking SAF to mortality in patients with severe AS are unknown, but are most likely related to the major neurohumoral adaptations that occur in heart failure, including activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system [23]. However, also additional mechanisms might be involved, including abnormal activation of autonomic cardiac reflexes, such as the Bezold–Jarisch reflex [24]. By assessing both tonic and reflex abnormalities of autonomic function, SAF might cover a wide spectrum of abnormal autonomic dysregulations that can occur in AS. HRT tests the responsiveness of the cardiovascular autonomic nervous system to intrinsic micro-disturbances in the form of VPCs which induce small, transient falls of arterial blood pressure [9,11]. Normal HRT requires an intact interplay among the vagal, sympathetic, and vascular systems [25]. DC is an integral measure of all deceleration-related oscillations of heart rate over 24 h related to respiratory, vascular, and humoral regulation processes [10]. Both HRT and DC capture different facets of autonomic control which facilitates making their combination such a strong risk predictor.

Table 5
Endpoints within 2 years in the 71 asymptomatic patients.

	All patients (n = 71)	SAF-negative (n = 59)	SAF-positive (n = 12)	p value
Primary endpoint				
All deaths (%)	10 (14.1)	4 (6.8)	6 (50.0)	<0.001
Secondary endpoints				
Cardiac deaths (%)	5 (7.0)	1 (1.7)	4 (33.3)	<0.001
Cardiac deaths & HF-related hospitalizations (%)	11 (25.5)	4 (6.8)	7 (58.3)	<0.001

HF — heart failure and SAF — severe cardiac autonomic failure. Patients who underwent aortic valve replacement or transcatheter aortic valve implantation during follow-up were censored at the date of operation.

The limitations of our study require mention. First, SAF assessment is not applicable to patients with atrial fibrillation [26]. Second, BNP levels were not available in 59 of the 216 symptomatic patients. However, prognosis of these patients did not differ from those in whom BNP levels were available ($p = 0.896$). Third, the number of endpoints in asymptomatic patients was small. We were therefore not able test the independency of SAF from other risk factors in this patient group. Forth, data on reproducibility of SAF are lacking which might limit the results of our study and clinical applicability of SAF as risk predictor in AS patients. As we did not re-assess SAF after intervention we also cannot comment on whether SAF might improve by effective treatment of AS. Both aspects need to be addressed by future studies. Fifth, it is known that pharmacological treatment may alter autonomic function including heart rate turbulence [27]. We therefore cannot exclude that pharmacological treatment of AS patients may have influenced SAF results. However, in our study we did not find a significant association between pharmacological treatment and the presence of SAF. Finally, although we have shown that SAF is a strong predictor of outcome we have no data at present to show that specific treatments guided by SAF will improve patients' prognosis.

In conclusion, the results of our study indicate that SAF is a strong and independent predictor of mortality in patients with severe AS. Future studies are needed to test whether implementation of SAF into current risk stratification concepts leads to a better outcome in patients with AS.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

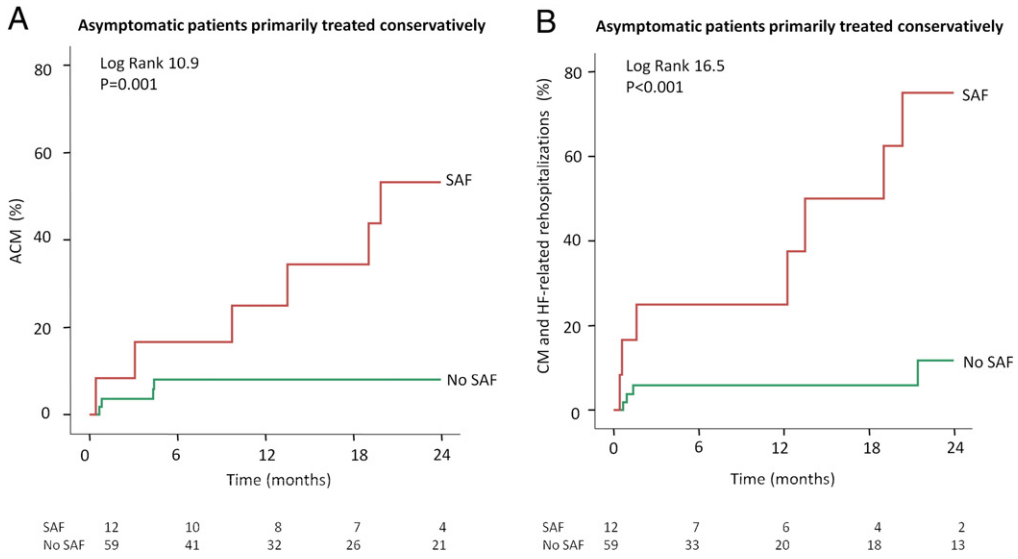

Fig. 3. Cumulative event rates of asymptomatic patients with severe aortic stenosis for whom a primarily conservative treatment strategy was proposed at study entry stratified by the presence of severe cardiac autonomic failure (SAF). Patients who underwent aortic valve replacement or transcatheter aortic valve implantation during follow-up were censored at the time of invasive treatment. (A) Primary endpoint (all-cause mortality) and (B) Secondary endpoint (composite of cardiac mortality and hospitalizations due to decompensated heart failure).

Acknowledgments

This work was supported by grants from the program "Angewandte Klinische Forschung" (AKF) of the University of Tübingen 252-1-0 and the "Deutsche Stiftung für Herzforschung F/13/12".

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Journal of Electrocardiology 50 (2017) 802 – 807

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Periodic repolarization dynamics in patients with moderate to severe aortic stenosis☆

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Abstract

Background: Periodic repolarization dynamics (PRD) refers to low-frequency oscillations of cardiac repolarization, most likely related to phasic sympathetic activation. Increased PRD is a validated predictor of mortality after myocardial infarction and in ischemic heart disease, but has not been tested in aortic valve stenosis (AS). Here, we assessed PRD in patients with AS and tested its correlation with clinical and hemodynamic parameters as well as markers of heart rate variability (HRV).

Materials and methods: We prospectively enrolled 139 consecutive patients with moderate to severe AS in sinus rhythm. In all patients we performed a 24-h Holter ECG in Frank–leads configuration. We assessed PRD according to previously published technologies from the nocturnal hours (0 am–6 am) and dichotomized PRD at the established cut-off value of ≥ 5.75 deg^2. In addition to clinical and hemodynamic markers, we also assessed deceleration capacity (DC) of heart rate, heart rate turbulence and standard HRV parameters.

Results: In the patients studied, PRD was 6.55 ± 3.96 deg^2. Seventy-three patients (52.5%) had increased PRD. Among them, 36 (49.9%) patients were classified as being asymptomatic. There was no association between increased PRD and clinical or hemodynamic markers, including presence of symptoms, NYHA-classification, aortic valve area, and left-ventricular ejection fraction. Thirty-three of the 73 (45.2%) patients with PRD ≥ 5.75 deg^2 also suffered from decreased vagal tonic activity by means of abnormal DC (≤ 2.5 ms) indicating severe autonomic dysfunction.

Conclusion: Prevalence of increased PRD is high among patients with moderate to severe AS. Patients with increased PRD cannot be identified by clinical or hemodynamic markers Future studies should test the prognostic value of PRD in patients with AS.

Keywords: Periodic repolarization dynamics; Sympathetic nervous system; Aortic stenosis

Introduction

Aortic valve stenosis (AS) is the most prevalent heart valve disorder and the third most common cardiovascular disease after coronary artery disease (CAD) and hypertension in developed countries [1]. The natural prognosis of AS varies widely, ranging from good to unfavorable. Therefore, accurate risk stratification is crucial for treatment decision. According to current guidelines an invasive treatment is delayed until development of symptoms or impairment of left-ventricular ejection fraction (LVEF) [2,3]. However, this "wait for symptoms" strategy might prove deleterious, as the symptomatic status cannot be reliably assessed especially in the elderly patients.

Increased sympathetic nervous system (SNS) activity is a sign of progression of the disease, which can be effectively reversed after trancatheter aortic valve replacement (TAVR) [4]. As AS worsens, cardiac output is reduced, and this situation leads to increased SNS activity, which finally predisposes to fatal cardiac arrhythmias and cardiac decompensation. As of yet, accurate assessment of SNS required an invasive approach using microneurographic measurements from the peroneal nerve [4].

Recently, we proposed a novel approach to non-invasively assess the effect of SNS-activity on the heart that substantially differs from previous methods [5]. So-called "Periodic Repolarization Dynamics (PRD)" evaluates sympathetic-activity-associated low-frequency periodic changes of cardiac repolarization and opens new perspectives for identifying

☆ Disclosures: All authors have declared that no conflict of interest exists.

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http://dx.doi.org/10.1016/j.jelectrocard.2017.08.004
0022-0736/

high-risk patients, which cannot be identified by other methods. PRD has been shown to be an important predictor of mortality and cardiovascular mortality in patients with acute [5] and chronic myocardial infarction (MI) [6]. Therefore, the aim of the present study is to evaluate PRD in patients with moderate to severe AS and to test its association with clinical and hemodynamic parameters, as well as markers of HRV. The present study is a substudy of the Risk Prediction in Aortic Stenosis study (PREDICT-AS; ClinicalTrials.gov number NCT01422044).

Material and methods

Study population

Between September 2009 to November 2012 we prospectively enrolled patients who presented for evaluation of known or suspected AS at the Eberhard-Karls-University of Tuebingen, Germany (Fig. 1). Eligible patients were in sinus rhythm and had moderate to severe AS (aortic valve area [AVA] ≤ 1.5 cm^2 and/or mean aortic pressure gradient ≥ 25 mm Hg), which was confirmed invasively or by echocardiography. Patients were excluded if they were not in sinus rhythm, if they had an acute coronary syndrome or significant coronary stenosis requiring revascularization, or when an additional hemodynamically significant valve lesion was present. In this post-hoc analysis we also excluded patients for whom a Holter ECG in Frank leads configuration was either not available or did not meet the standards for PRD assessment.

Assessment of periodic repolarization dynamics

In all patients, 24-h Holter recordings (Cardio CM 3000, Getemed, Teltow, Germany) were performed in Frank leads configuration at a sample rate of 256 Hz. As long as PRD assessment requires standardized conditions in supine, resting position, we only used the nocturnal phase between 00 a.m. to 06 a.m. for evaluation of PRD. The technical details of PRD assessment have been described elsewhere [5]. Briefly, X-,Y- and Z–leads are converted to a set of polar coordinates defined by two angles (azimuth and elevation) and the amplitude Amp. We used established algorithms in order to define the beginning and ending of each T-wave [7]. In a second step, we integrated the spatiotemporal characteristics of each T-wave into a single vector $T°$, which is defined by the so-called weight-averaged azimuth (WAA) and weight-averaged elevation (WAE):

$$Weight\ Averaged\ Azimuth\ (WAA) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * Azimuth_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (1)$$

$$Weight\ Averaged\ Elevation\ (WAE) = \frac{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t * Elevation_t)}{\sum_{t=T_{start}}^{t=T_{end}} (Amp_t)} \quad (2)$$

In a third step, we estimated the instantaneous degree of repolarization instability by means of the angle $dT°$ between successive repolarization vectors. $dT°$ was calculated using

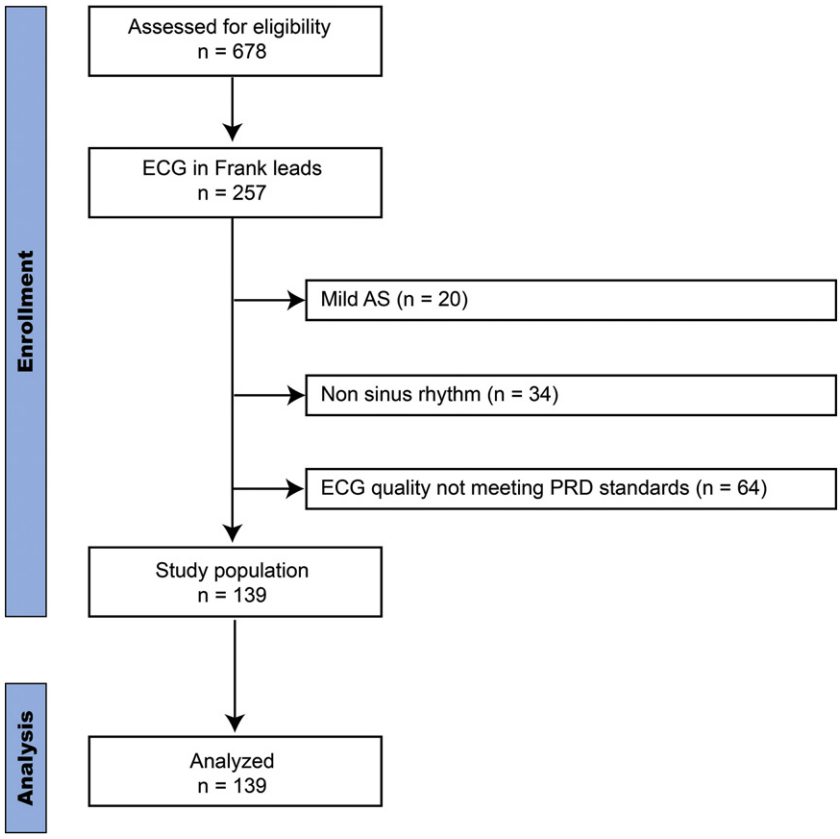

Fig. 1. Consort flow-diagram for patient selection. AS = aortic stenosis.

the scalar product of two successive repolarization vectors $T°$ according to Eq. (3) [5, Supplemental Fig. 6].

$$dT^{\circ} = acos[\ \sin(WAE_1) * \cos(WAA_1) * \sin(WAE_2) * \cos(WAA_2) + \cos(WAE_1) * \cos(WAE_2) + \sin(WAE_1) * \sin(WAA_1) * \sin(WAE_2) * \sin(WAA_2)] \quad (3)$$

We finally applied continuous wavelet transformation on the $dT°$-signal and quantified PRD as the average wavelet coefficient corresponding to frequencies of ≤ 0.1 Hz [5]. PRD was dichotomized at the established cut-off value of ≥ 5.75 deg^2.

Assessment of heart rate variability

Standard HRV parameters were calculated in time and frequency domains according to the Task Force of the European society of Cardiology [8]. For this study the following standard HRV parameters were considered: mean heart rate (MHR), standard-deviation of all normal-to-normal intervals (SDNN), square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals (RMSSD), heart rate variability index (HRVi), spectral power in the low-frequency range (LF), spectral power in the high-frequency range (HF) and the LF/HF ratio. In addition to the standard HRV parameters we also calculated heart rate turbulence (HRT) and deceleration capacity of heart rate (DC) according to previously published technologies [9,10]. Briefly, HRT refers to the biphasic physiological response of heart rate following a spontaneous ventricular premature contraction (VPC) and is composed of an initial heart rate acceleration followed by a subsequent heart rate deceleration. The two phases of HRT can be quantified by two numerical parameters: turbulence onset (TO) and turbulence slope (TS). Here, HRT was considered abnormal if both TO and TS were abnormal (HRT category 2; TO ≥ 0% and TS $\leq$ 2.5 ms/RR interval [11]). If a patient had no VPCs, HRT was defined as normal. DC is an integral measure of all deceleration-related oscillations of heart rate, related to tonic vagal activity. Calculation of DC is based on the transformation of the sequence of RR intervals into a new time series by phase-rectified signal averaging (PRSA). The central deflection of the PRSA signal characterizes the average capacity of the heart to decelerate and can be quantified by Haar wavelet analysis using a scale of 2 ($T = 1$). DC ≤ 2.5 ms was considered abnormal [10]. All HRV parameters, with exception of HRT, were evaluated during the nocturnal phase. HRT was assessed from the entire recording, as it is influenced from the total number of VPCs, which are normally reduced during the night hours.

Assessment of clinical markers

Patients were classified as being symptomatic if at least one of the following findings were present: syncope; angina pectoris (Canadian Cardiovascular Society [CCS] grading $\geq$ II) or heart failure (New York Heart Association [NYHA] functional class $\geq$ II). All other patients were classified as being asymptomatic. Glomerular filtration rate (GFR) was calculated by means of the Cockroft-Gault formula. Renal insufficiency was defined as GFR < 60 ml/min/1.73 m^2. The presence of chronic obstructive pulmonary disease (COPD) was defined by long term use of bronchodilators or steroids for lung disease. Extracardiac arteriopathy was considered present if the patient suffered from claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids. Logistic euro-SCORE was calculated as previously described [12].

Assessment of hemodynamic markers of aortic stenosis

In all patients, following hemodynamic variables were assessed using echocardiography or invasive measurement: LVEF, AVA, peak and mean aortic pressure gradient and systolic pulmonary artery pressure (PAP_{sys}). In patients undergoing left and right heart catheterization, hemodynamic variables were obtained invasively, as follows: LVEF was obtained by the area-length method from a single- plane right anterior oblique projection, PAP_{sys} was obtained using a 7F Swan-Ganz catheter and AVA was calculated using the Gorlin formula. In patients in whom no catheterization was performed, hemodynamic variables were obtained by echo-cardiography (iE33, Philips Medical Systems). In these patients, LVEF was assessed by the modified Simpson rule with images obtained from apical 4- and 2-chamber views. AVA was estimated by the continuity equation using the velocity–time integral of the aortic and left ventricular outflow tract flows and PAP_{sys} was estimated using the tricuspid pressure gradient by adding mean right arterial pressure derived from the inferior vena cava absolute diameter and diameter change during inspiration.

Statistical analysis

Continuous variables are expressed as means with standard deviations and are compared using the Wilcoxon rank sum test. Categorical data are presented as percentages and are analyzed using the chi-square test. Correlations between continuous variables were assessed by Pearson's product-moment correlation coefficient. To compare PRD between AS and MI we performed propensity score matching analysis using the Autonomic Regulation Trial [5] as matching population. Propensity scores were generated by logistic regression analysis and a nearest-neighbour matching techinque was applied [13]. The variables used to estimate the propensity score were age and gender. Differences were considered statistically significant when the two-sided p-value was <0.05. All statistical analyses were performed using CRAN R 3.2.3.

Results

As shown in Fig. 2, typical low-frequency oscillations of cardiac repolarization could also be detected in patients with moderate to severe AS (Fig. 2). In the patients studied, PRD was 6.55 ± 3.96 deg^2. Seventy three of the 139 patients (52.5%) were classified as abnormal, based on PRD ≥ 5.75 deg^2. Using propensity score matching analysis for age and gender we selected 70 patients with AS (mean age = 71.4 ± 7.4 years; 32 females) and 70 post-MI patients from the Autonomic

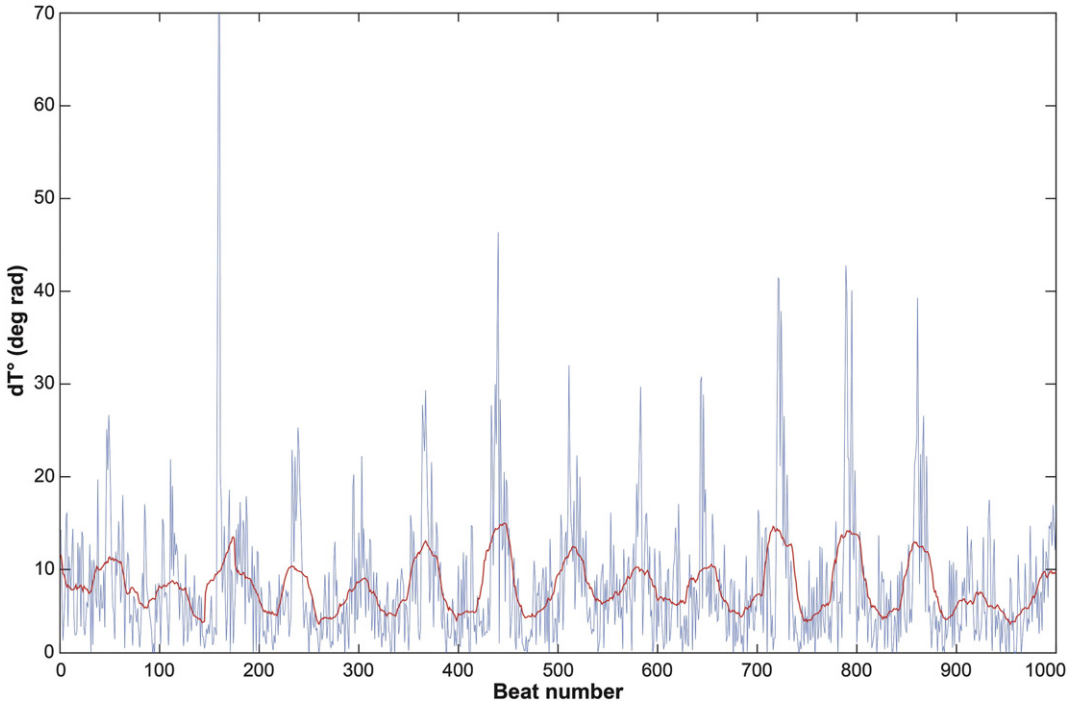

Fig. 2. Typical $dT°$ signal with characteristic low-frequency oscillations of repolarization obtained from a patient with moderate to severe aortic stenosis and increased periodic repolarization dynamics (PRD) (7.87 deg^2). For illustration purposes only 1000 heart beats are plotted.

Regulation Trial (mean age = 71.8 ± 7.2 years; 27 females; $p = 0.737$ for age and $p = 0.494$ for gender). PRD was significantly higher in AS patients (6.04 ± 3.80 deg^2) compared to post-MI patients (5.06 ± 4.24 deg^2; $p = 0.019$). Table 1 depicts baseline and clinical characteristics as well as hemodynamic parameters in patients with moderate to severe AS stratified by PRD. Of particular note, there were no significant differences in clinical and hemodynamic markers between patients with normal and abnormal PRD.

Table 2 shows the correlation between PRD and parameters of HRV. Increased PRD was associated with increased MHR ($r = 0.36$ [0.21–0.50]), decreased DC ($r = -0.42$ [−0.55 to −0.27]) and increased LF ($r = 0.31$ [0.15–0.46]) and HF 0.30 [0.14–0.45]. Thirty-three of the 73 (45.2%) patients with increased PRD also suffered from decreased DC ≤2.5 ms. The mean nocturnal heart rate among patients was significantly higher in patients with increased PRD (71 ± 11 bpm) compared to patients with

Table 1
Baseline, clinical characteristics and hemodynamic parameters.

	All patients	PRD < 5.75 deg^2	PRD ≥ 5.75 deg^2	*p*-value
Baseline and clinical characteristics				
Number of patients, n (%)	139	66 (47.5)	73 (52.5)	
Age, years (SD)	78.0 (8.8)	77.3 (8.7)	78.6 (8.9)	0.225
Females, n (%)	79 (56.8)	35 (53.0)	44 (60.3)	0.490
Severe AS, n (%)	105 (75.6)	49 (74.2)	56 (76.7)	0.888
Symptoms, n (%)	81 (58.3)	44 (66.7)	37 (50.1)	0.083
Hypertension, n (%)	111 (79.9)	51 (77.2)	60 (82.2)	0.610
Diabetes mellitus, n (%)	48 (34.5)	23 (34.8)	25 (34.2)	0.999
CAD, n (%)	84 (60.4)	43 (65.2)	41 (56.2)	0.364
Previous MI, n (%)	20 (14.4)	9 (13.6)	11 (15.1)	0.999
NYHA-Class ≥ III, n (%)	21 (15.1)	10 (15.2)	11 (15.1)	0.999
Renal insufficiency, n (%)	43 (30.9)	20 (30.3)	23 (31.5)	0.999
COPD, n (%)	9 (6.5)	5 (7.6)	4 (5.5)	0.876
Logistic euroScore, % (SD)	15.8 (13.8)	13.5 (9.7)	17.9 (16.4)	0.269
Hemodynamic parameters				
AVA, cm^2 (SD)	0.77 (0.27)	0.76 (0.28)	0.78 (0.24)	0.823
Mean gradient, mmHg (SD)	39.0 (20.1)	38.2 (17.7)	39.6 (22.1)	0.815
Peak gradient, mmHg (SD)	58.1 (31.8)	58.0 (28.8)	58.2 (34.4)	0.741
LVEF, % (SD)	51 (11)	51 (11)	52 (11)	0.772
PAP_{sys}, mmHg (SD)	33 (15)	32 (13)	34 (16)	0.491

AS = aortic stenosis; AVA = aortic valve area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LVEF = left-ventricular ejection fraction; NYHA = New York Heart Association; PAP_{sys} = systolic pulmonary artery pressure; PRD = periodic repolarization dynamics.

Table 2
Correlation between PRD and markers of heart rate variability.

	Mean (SD)	Correlation coefficient with PRD (95% CI)	*p*-value
Mean heart rate, bpm	68 (11)	0.36 (0.21–0.50)	<0.001
SDNN, ms	78 (35)	0.13 (−0.04–0.29)	0.142
RMSSD, ms	25 (15)	0.13 (−0.04–0.29)	0.133
HRVi, U	32 (14)	0.05 (−0.12–0.22)	0.542
DC, ms	2.66 (6.28)	−0.42 (−0.55 to −0.27)	<0.001
LF, ms^2	678 (928)	0.31 (0.15–0.46)	<0.001
HF, ms^2	218 (245)	0.30 (0.14–0.45)	<0.001
LF/HF ratio	3.6 (3.5)	0.02 (−0.14–0.19)	0.792

DC = deceleration capacity of heart rate; bpm = beats per minute; HRVi = heart rate variability index; HF = spectral power in the high-frequency range; LF = spectral power in the low-frequency range; RMSSD = square root of the mean of the sum of squared differences between adjacent normal-to-normal intervals; SDNN = standard-deviation of all normal-to-normal intervals.

normal PRD (65 ± 10 bpm; $p = 0.005$). PRD was evenly distributed among patients with normal (6.69 ± 4.05 deg^2) and abnormal HRT (5.89 ± 3.47 deg^2; $p = 0.465$).

Discussion

The findings of our study indicate that increased sympathetic activity quantified by means of PRD was a common finding among patients with AS. Its prevalence (52.5%) is substantially higher compared with other patient populations, e.g. post-MI patients where the prevalence of increased PRD was estimated at 25% [5]. Interestingly, the group of patients identified by increased PRD could not be detected by conventional clinical and hemodynamic markers, with almost half of the patients with increased PRD being asymptomatic.

The exact mechanisms underlying PRD need further investigation. However, there is a body of evidence that PRD reflects the effect of sympathetic activity on ventricular myocardium. First, PRD mimics the characteristic low-frequency pattern of efferent sympathetic activity [14,15], which can be also found in many other biosignals, including heart rate, blood pressure, and microneurographic measurements of muscle sympathetic nervous system activity (MSNA). Second, physiological and pharmacological studies showed that provocations such a tilt test or exercise led to an increase of PRD in healthy individuals, while pharmacological blockade of the sympathetic nervous system by beta-blockers resulted to a significant suppression of PRD [5]. Third, Hanson et al. could demonstrate an oscillatory behavior of ventricular action potential duration (APD) in the same low-frequency range in patients with heart failure [16]. Using a modeling study the same group could show that these low-frequency oscillations were enhanced by phasic beta-adrenergic stimulation and phasic mechanical stretch. In the presence of calcium overload and reduced repolarization reserve, both characteristics of heart failure, these oscillations predisposed to early afterdepolarizations and arrhythmic events [17]. The presence of sympathetic overactivity in patients with severe AS has been already demonstrated using invasive MSNA measurements [4]. Although the prognostic value of increased SNS activity in patients with AS needs further investigation it is reasonable to suppose that it is a sign of progression of the disease, which leads to a counterbalancing SNS activation. More importantly this sympathetic overactivity can be effectively reversed after TAVR [4].

PRD, as a marker of increased sympathetic activity was associated with increased nocturnal heart rate in this study. The correlation between PRD and DC indicates that there is a group of patients with AS suffering from both, sympathetic and vagal autonomic dysfunction. In post-MI patients, combined vagal and sympathetic dysfunction is associated with poor outcome. We performed a post-hoc analysis in the Autonomic Regulation Trial [5] and found that post-MI patients with PRD ≥ 5.75 deg^2 and DC ≤ 2.5 ms (10.7% of the patients) had a 5-year mortality rate of 30.1%, compared to a 2.9% 5-year mortality rate among patients with normal PRD and DC (65.6% of the patients). In the population of patients with AS we could identify 33 patients (23.7%) with abnormal PRD and DC, which is substantially higher compared to the post-MI population.

Zuern et al. [18] report a six fold increased risk of 2-year mortality in patients with severe AS and combined abnormalities of DC and HRT, so-called “severe autonomic failure” (SAF). In this study, there was no significant difference in the level of PRD between patients with normal and abnormal HRT, which implies that increased PRD might detect a different population than abnormal HRT. Although both HRT and PRD are influenced by increased SNS activity, this regulation takes place at different levels. While HRT quantifies the baroreflex-mediated SNS activation to the transient fall of arterial pressure caused by a VPC [9], PRD detects the response of the ventricular myocardium to phasic sympathetic activation.

Assessment of PRD requires a three-dimensional, high-quality ECG recording. The algorithm of PRD is very sensitive in detecting small changes in the amplitude, direction or duration of repolarization, which cannot be identified by conventional repolarization markers. Low-frequency oscillations of repolarization can be also detected from single–lead recordings by applying the PRD algorithm on the QT-interval. Although this method might be much simpler in nature, a post-hoc analysis in the Autonomic Regulation trial [5] has shown that it is associated with a lower predictive power for predicting mortality (area under the curve [AUC] 0.67 [95% CI 0.60–0.73], $p < 0.001$ vs. 0.73 [95% CI 0.66–0.79], $p < 0.001$) for PRD and cardiovascular mortality (AUC 0.66 [95% CI 0.57–0.75], $p = 0.001$ vs. 0.72 [95% CI 0.62–0.81], $p < 0.001$ for PRD).

The limitations of our study require mention. First, we assessed PRD from Holter ECGs during the night hours, while in the seminal study PRD was assessed from 30-min recordings in standardized conditions. Second, patients with atrial fibrillation were not included in this study, as is presently unknown whether PRD can also be applied to patients with atrial fibrillation. Third, the proposed cut-off value of PRD originates from a post-MI population. Additional studies are needed to test whether this cut-off value also applies to patients with AS.

In conclusion, the results of our study indicate that calculation of PRD is feasible among patients with moderate to severe AS and can identify a group of patients with increased SNS activity who cannot be detected by conventional clinical and hemodynamic markers. Future studies are needed to evaluate the prognostic value of PRD in AS patients.

Acknowledgements

PREDICT-AS was supported by grants from the program "Angewandte Klinische Forschung" (AKF) of the University of Tübingen 252-1-0 and the "Deutsche Stiftung für Herzforschung F/13/12".

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Implantable cardiac monitors in high-risk post-infarction patients with cardiac autonomic dysfunction and moderately reduced left ventricular ejection fraction: Design and rationale of the SMART-MI trial

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Background Most deaths after myocardial infarction (MI) occur in patients with left ventricular ejection fraction (LVEF) >35%, for whom no specific prophylactic strategies exist. Deceleration capacity (DC) of heart rate and periodic repolarization dynamics (PRD) are noninvasive electrophysiological markers depending on the vagal and sympathetic tone. The combination of abnormal DC and/or PRD identifies a new high-risk group among postinfarction patients with LVEF 36%-50%. This new high-risk group has similar characteristics with respect to prognosis and patient numbers to those of the established high-risk group identified by LVEF ≤ 35%.

Study design The SMART-MI trial is an investigator-initiated randomized prospective multicenter trial that tests the efficacy of implantable cardiac monitors (ICM) in this new high-risk group. The study will enroll approximately 1,600 survivors of acute MI with sinus rhythm and an LVEF of 35%-50% in 17 centers in Germany who will be tested for presence of cardiac autonomic dysfunction. Four hundred patients with either abnormal DC (≤2.5 ms) and/or PRD (≥5.75 deg^2) will be randomized in a 1:1 fashion to intensive follow-up via telemonitoring using an ICM device (experimental arm) or conventional follow-up (control arm). For the ICM arm, specific treatment paths have been developed according to current guidelines.

Outcomes The primary end point is time to detection of predefined serious arrhythmic events during follow-up, including atrial fibrillation ≥6 minutes, nonsustained ventricular tachycardia (cycle length ≤320 ms; ≥40 beats), atrioventricular block ≥IIb, and sustained ventricular tachycardia/ventricular fibrillation. The median follow-up period is 18 months with a minimum follow-up of 6 months. The effect of remote monitoring on clinical outcomes will be tested as secondary outcome measure (ClinicalTrials.gov NCT02594488). (Am Heart J 2017;190:34-9.)

Background and rationale

Sudden cardiac death (SCD) is the leading single cause of death in the industrialized world.[1] Survivors of an acute myocardial infarction (MI) are at increased risk for SCD. Randomized controlled trials demonstrated that in high-risk patients after MI mortality can be reduced by prophylactic interventions including implanted cardioverter/defibrillator implantation.[2,3] In these trials, the criterion of a reduced left ventricular ejection fraction (LVEF ≤ 35%) was used to identify high-risk post-MI patients.[4] Accordingly, current guidelines consider post-MI patients with LVEF ≤ 35% for prophylactic ICD implantation, disregarding the fact that most patients who die after MI have LVEF > 35%. Indeed in a recent prospective cohort study including 2,343 post-MI patients, only 57 (31%) of 181 deaths during a 5-year follow-up occurred in patients with LVEF ≤ 35%.[5] Although overall cardiovascular mortality is declining, the incidence of SCD over the last decades remained unchanged.[6] These and other data stress the importance of alternative approaches to identify high-risk post-MI patients, especially among those with LVEF > 35%, for guidance of prophylactic therapies. (See Fig).

Experimental and clinical studies indicated that important prognostic information after MI can be derived from the functional status of the cardiac autonomic nervous system.[7] Both increased sympathetic and depressed vagal

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RCT No. NCT02594488
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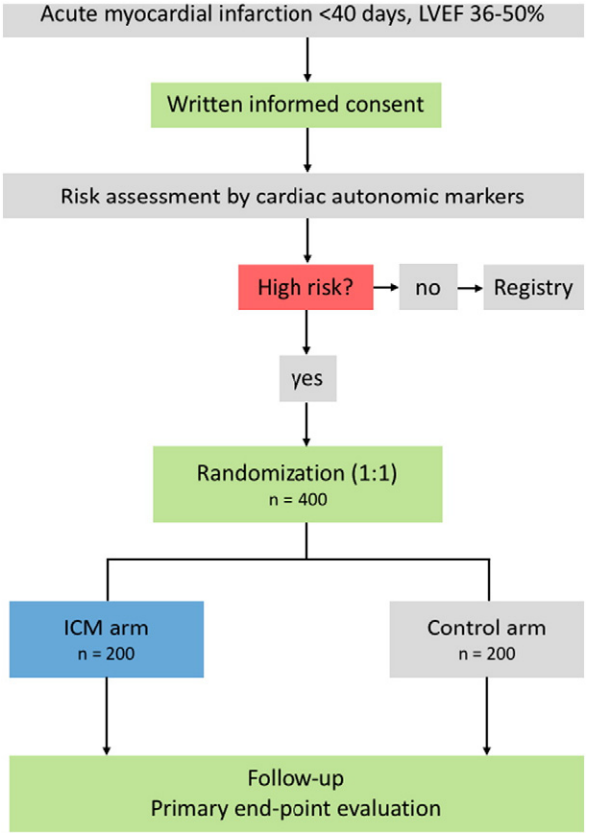
http://dx.doi.org/10.1016/j.ahj.2017.05.006

Figure



Flowchart of the SMART-MI study.

activity after MI have been associated with an increased susceptibility to malignant bradyarrhythmia and tachyarrhythmia eventually culminating in SCD.[8]

Deceleration capacity (DC) of heart rate and periodic repolarization dynamics (PRD) are clinically validated electrocardiogram (ECG)-based autonomic risk markers that provide strong and independent prognostic information in post-MI patients with LVEF > 35%.[9,10] Deceleration capacity and PRD reflect different facets of autonomic function and can therefore be used in combination to predict risk. Deceleration capacity is an integral measure of autonomic, predominantly vagally mediated regulations of heart rate.[9] Periodic repolarization dynamics captures previously unknown low-frequency (<0.1 Hz) oscillations of cardiac repolarization related to sympathetic activation.[10] In a previous study, combined assessment of PRD and DC identified a new high-risk group among post-MI patients with moderately reduced LVEF (36%-50%).[11] This new high-risk group has similar characteristics with respect to prognosis and patient numbers to those of the established high-risk group identified by LVEF ≤ 35%. Although the poor prognosis of post-MI patients with autonomic dysfunction is well established, the exact mode of death in these patients is still unknown. Particularly, a better understanding of the association with serious arrhythmic events is of crucial importance to initiate specific preventive strategies in this high-risk group.

As known from studies with implantable cardiac monitors (ICMs) in post-MI patients with LVEF ≤ 40%, eventual death is often preceded by primarily asymptomatic arrhythmic events, including new-onset atrial fibrillation, nonsustained ventricular tachyarrhythmias, and higher-degree atrioventricular (AV) block.[12] This suggests a potential time frame for preemptive interventions in case of early detection of arrhythmic events, which could improve outcome.

The "Implantable cardiac monitors in high-risk post-infarction patients with cardiac autonomic dysfunction and moderately reduced left ventricular ejection fraction (SMART-MI)" study will assess the efficacy of ICMs in detecting serious arrhythmic events in the high-risk group of post-MI patients with moderately reduced LVEF (36%-50%) and autonomic dysfunction. The effect of home monitoring on clinical outcomes will be tested as a secondary end point. This article presents the rationale and design of the SMART-MI trial.

Methods

Study design

The SMART-MI study (ClinicalTrials.org NCT02594488) is a multicenter, randomized, open-labeled clinical trial. Survivors of acute MI <40 days with LVEF 36%-50% and in sinus rhythm undergo risk stratification by means of DC and PRD assessed from a 20-minute resting ECG. High-risk patients will be 1:1 randomized. The experimental arm consists of intensified surveillance and follow-up by means of an ICM (Reveal LINQ; Medtronic, Ireland) with home-monitoring capability. The control arm of the study consists of conventional follow-up as recommended by current guidelines.[13] In all study patients, a blood sample for bio-banking is obtained. Low-risk patients will enter a registry. Figure summarizes the study flow of patients within the trial. The primary end point is time to detection of serious arrhythmic events during follow-up as defined below. End points will be adjudicated by an event adjudication committee blinded to the patients' allocation. Seventeen centers in Germany, among them 15 university centers, will participate in this trial. The inclusion and exclusion criteria are outlined in Table I.

The following baseline procedures will be performed before randomization: targeted medical history and physical examination, including pulse, blood pressure, height, and weight (body mass index); 12-lead ECG; echocardiography (>48 hours after index MI or when CK-MB has normalized) for assessment of LVEF; screening laboratory tests: white blood cell count, hemoglobin,

Table I. Inclusion and exclusion criteria

Inclusion criteria
Acute MI <40 d: STEMI and NSTEMI according to definition by current ESC guidelines with evidence of coronary lesion on coronary angiogram requiring PCI
LVEF 36%-50% as assessed by echo, LV angiogram, or MRI; >48 h after index MI or when CK-MB has normalized
Evidence of cardiac autonomic dysfunction: abnormal heart rate DC <2.5 ms and/or abnormal PRD ≥5.75 deg^2 >48 h after index MI or when CK-MB has normalized
Age 18-80 y
Sinus rhythm
Optimal medical therapy
Written informed consent
Exclusion criteria
Indication for ICD or pacemaker
Known paroxysmal or persistent atrial fibrillation
Life expectancy <12 mo
Inability to comply with follow-up
Pregnancy
Participation in another trial that may interfere

Abbreviations: *STEMI*, ST-segment elevation MI; *NSTEMI*, non–ST-segment elevation MI; *ESC*, European Society of Cardiology; *PCI*, percutaneous coronary intervention; *LV*, left ventricular.

Table II. Primary and secondary end points

Primary end point: composite of predefined arrhythmias
Atrial fibrillation ≥6 min
Higher-degree AV block ≥IIb
Ventricular tachycardia with a cycle length ≤320 ms lasting for ≥12 s (corresponding to 40 beats)
Sustained VT and VF
Secondary end points
Composite of all-cause mortality, stroke, systemic arterial thromboembolism, and unplanned hospitalizations for decompensated heart failure
All-cause mortality
Cardiovascular mortality
Unplanned hospitalizations for decompensated heart failure
Sinus arrest >6 s
Nonsustained VT ≥16 beats
Bradycardias as defined above
Ventricular arrhythmias as defined above
Quality of life
Device-related complications including infections and major bleedings (BARC ≥2)

hematocrit, platelet count, serum creatinine, electrolytes, activated partial thromboplastin time, international normalized ratio, CK and its MB fraction, and troponin-T or troponin-I; and 20-minute resting ECG for assessment of cardiac autonomic markers (>48 hours after index MI or when CK-MB has normalized).

Study outcomes

The primary end point is time to detection of the following predefined serious arrhythmic events (Table II), including atrial fibrillation ≥6 minutes, higher-degree AV block (≥IIb, ie, second-degree AV block type 2 and third-degree AV block), nonsustained ventricular tachycardia (VT) with a cycle length ≤320 ms lasting for ≥12 seconds (corresponding to 40 beats),[14] and sustained VT/ventricular fibrillation (VF).

All of the predefined arrhythmias have been associated with adverse clinical events in previous studies or indicate a proven criterion for delivering ATPs in patients with implanted ICDs.[12,14,15]

Secondary outcomes include the following: the composite of all-cause mortality, stroke, systemic arterial thromboembolism, and unplanned hospitalizations for decompensated heart failure; all-cause mortality; cardiovascular mortality; unplanned hospitalizations for decompensated heart failure; sinus arrest >6 seconds; nonsustained VT ≥16 beats; bradycardias as defined above; ventricular arrhythmias as defined above; quality of life; and device-related complications including infections and major bleedings (bleeding Academic Research Consortium [BARC] ≥2) (Table II).

Assessment of cardiac autonomic markers and risk stratification

A 20-minute resting ECG for assessment of DC and PRD will be performed >48 hours after index infarction or when CK-MB has normalized. Electrocardiogram raw signals are digitally transferred to an ECG core laboratory (LMU Munich) for standardized computation of DC and PRD.[9,10] Patients with either abnormal DC (≤2.5 ms) or abnormal PRD (≥5.75 deg^2) will be classified as high-risk patients.

Implantable cardiac monitors

In patients randomized to the ICM arm, a commercially available, CE-marked ICM (Medtronic Reveal LINQ) will be subcutaneously implanted using local anesthesia according to local standard operating procedures. The ICM is capable of automatic detection of predefined arrhythmias, which will be telemetrically transferred to an ICM core laboratory (LMU Munich) on a daily basis. Arrhythmia detection parameters of the ICMs are set as recommended in the operating manual with "AF management" chosen as reason for monitoring. All detected arrhythmias are immediately checked by an experienced physician in the core laboratory. True-positive findings meeting the predefined criteria of the primary end point (see above) are reported to the local study centers within 48 hours. Treatment paths for different kind of arrhythmias have been developed in line with current guidelines. However, final treatment decisions are left to the local treating physician.

Randomization and follow-up

After all inclusion criteria have been confirmed, patients will be randomized (according to a predefined block randomization list with random block sizes between 4 and 8) between ICM and conventional follow-up with a randomization sequence of 1:1. Allocation to treatment will be made by means of a Web-based computer-generated sequence with stratification according to study center, age, and LVEF. The 2 treatment groups will be studied concurrently. *Time zero* is defined as the time of randomization. Patients will be considered enrolled in the study and eligible for the final intention to treat analysis at time of randomization.

Outpatient study visits are scheduled every 6 months. A 12-lead ECG will be recorded and patients will be evaluated for the occurrence of following events: MI, stroke, systemic thromboembolism, unplanned hospitalization, bleeding, infection, and arrhythmic events. In patients with ICMs, the device will be interrogated. At 12 and 24 months, a 20-minute resting ECG will be performed for reevaluation of cardiac autonomic function.

The enrollment period is planned for 24 months with a minimum follow-up of 6 months and a medium follow-up of 18 months.

Safety monitoring

Events relevant for safety will be assessed by the site principal investigator and will be confirmed by 2 members of the Event Adjudication Committee blinded to the patient's allocation. Device-related complications and major bleeding (BARC $\geq$2) will be used as trial safety parameters. Events will be reported to the Safety Monitoring Board.

Ethical conduct

The SMART-MI trial will be conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization "Good Clinical Practices," and the respective national regulations. Participating centers have to provide written approval of the institutional medical ethics committee. Implantable cardiac monitors used in this trial have a CE mark, are approved by the Food and Drug Administration, and are market released.

Statistical analysis

A total sample size of 400 patients is expected to achieve 90% power to detect a statistically significant difference ($P \leq .05$) in time to first arrhythmic event. Calculation of sample size is based on an annual event rate of 5% in the control arm and 13% in the ICM arm.[12] With these event rates, a total of 46 events are required in both arms combined. The sample size calculation further considers a dropout rate of 15% (including deaths as well as patients refusing to continue follow-up).

The main analyses will test superiority of the ICM arm with respect to early detection of serious arrhythmic events based on a time-to-event analysis. The intergroup difference for the primary end point will be assessed by a proportional hazards model. Because death may be related to the events that determine the primary end point, an independent censoring is not reasonable if death takes place. Therefore, death will be introduced as competing risk. The analysis will be based on the cause-specific hazard approach. A proportional cause-specific hazards model is used to assess the difference in event detection speed between both trial arms. Aalen-Johansen estimators are used to represent the cause-specific cumulative event probabilities in both treatment groups. CIs for the hazard ratio will be calculated. The analysis allows for stratification with respect to age (<70 years/$\geq$70 years) and LVEF (<45%/$\geq$45%). Centers will be represented by a random effect (frailty). We will present continuous data by mean ± SD or median and interquartile range, as appropriate. Categorical data will be presented as rate and percentage. Depending on the normality of distribution, we will compare continuous variables by the Student t test or the Wilcoxon test, as appropriate. Categorical data will be compared using the χ^2 test. Missing values in baseline variables will be imputed following the MAR approach. The analysis of secondary end points will use standard proportional hazards models for the mortality as well as the composite event end point. Cause-specific hazard models will be used to analyze secondary end points where appropriate.

Timelines

The first SMART-MI patient was enrolled May 2016. At the time of submission of this manuscript, 43 patients have been randomized (20 patients in the ICM arm, 23 patients in the control arm). Completion of recruitment is expected by May 2018, and the last patient visit by November 2018. First results of the main analysis should be available by February 2019.

The study is predominantly funded by the Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK). Medtronic covers expenses for the ICM devices including remote monitoring capabilities as well as staff expenses. Medtronic has no role in the study design, data collection, data analysis, data interpretation, or writing of reports.

Discussion

SMART-MI is a phase III/IV early clinical trial that tests the efficacy of ICMs in detection of serious arrhythmic events in a new high-risk group of postinfarction patients with LVEF 35%-50% and presence of cardiac autonomic dysfunction.

Implantable cardiac monitors are typically implanted for different indications, either to reveal the underlying cause of unexplained syncope,[16] to assess the burden of atrial fibrillation after ablation,[17] or to screen patients with cryptogenic stroke for presence of atrial fibrillation.[18] Assessment of arrhythmic risk after MI is presently not considered a typical indication for ICM implantation. In fact, there are only 2 studies in which ICMs have been implanted for this specific indication. The nonrandomized CARISMA study included 297 survivors of acute MI with reduced LVEF (≤40%) who underwent ICM implantation.[12] During a 2-year follow-up, predefined bradyarrhythmia and tachyarrhythmia were detected in 46% of the patients (n = 137). The investigators of CARISMA documented a 28% incidence of new-onset atrial fibrillation (≥16 beats; frequency ≥ 125 beats/min), a 13% incidence of nonsustained VT, a 10% incidence of high-degree AV block, a 7% incidence of sinus bradycardia, a 5% incidence of sinus arrest, a 3% incidence of sustained VT, and a 3% incidence of VF, respectively. Most arrhythmias (86%) were asymptomatic but had important prognostic and therapeutic implications. Among the different kinds of arrhythmias, high-degree AV block was the most significant predictor of subsequent death. New-onset atrial fibrillation occurred with a 4-fold higher incidence than expected and was associated with an increased risk of developing ventricular bradyarrhythmia and tachyarrhythmia.[19] Interestingly, presence of cardiac autonomic dysfunction at baseline predicted both new-onset atrial fibrillation[20] and higher-degree AV block[21] with a hazard ratio of up to 7.0 and 6.0, respectively. In the nonrandomized ARREST study,[22] 50 patients after acute MI with an LVEF ≥40% underwent ICM implantation. New-onset atrial fibrillation (≥2 minutes) could be detected in 29 patients, with 27 being asymptomatic. In contrast, asystoles and VTs could only be detected in 4 and 3 patients, respectively. It should be noted, however, that in both the CARISMA and ARREST studies, the criteria for detection of atrial fibrillation were very sensitive.

SMART-MI now uses ICMs to address a new high-risk group of postinfarction patients that is not considered by current guidelines. Although approximately 70% of deaths after MI occur in postinfarction patients with LVEF > 35%, no specific preventive strategies exist for this large patient group. Autonomic risk stratification by DC and PRD is capable of separating a high-risk group of postinfarction patients with LVEF 35%-50% that equals the established high-risk group with LVEF ≤ 35% with respect to sample size and prognosis. Both markers can be obtained from 20-minute high-resolution resting ECGs recorded in the orthogonal Frank leads configuration. The underlying algorithms could be easily implemented in existing ECG systems. We estimate that in our study, 4 postinfarction patients with LVEF 35%-50% need to be tested to identify 1 patient with abnormal DC and/or PRD. Although the strong prognostic value of DC and PRD is not restricted to patients with LVEF ≤ 50%, we used the upper threshold of LVEF to reduce the screening effort.

The primary end point of SMART-MI is a diagnostic end point, which also determines the sample size calculation. Predefined arrhythmias include 4 different types of arrhythmias that all have been associated with adverse events in large clinical studies or represent indications for ATPs in patients with implanted ICDs. In the ASSERT study, atrial fibrillation >6 minutes has been associated with a 2.5-fold risk of stroke or systemic thromboembolism.[15] Detection of asymptomatic atrial fibrillation challenges the question of oral anticoagulation in many patients. Although a recent post hoc analysis of the ASSERT study indicated increased risk of stroke only in patients with episodes of asymptomatic atrial fibrillation lasting longer than 24 hours,[23] ongoing large-scale randomized trials including the ARTESIA trial (NCT01938248) and the NOAH-AFNET 6 trial (NCT02618577) test the efficacy of oral anticoagulation in patients with episodes >6 minutes. In patients after acute MI, new-onset atrial fibrillation might have additional implications as it might reflect beginning cardiac deterioration.[12] In CARISMA, higher-degree AV block was associated with a 6.6-fold risk of death[12] and might not only indicate pacemaker implantation but also a careful diagnostic workup for underlying problems. A VT with a cycle length ≤320 ms lasting for 12 seconds or more is a proven criterion for ATPs in patients with implanted ICDs.[14] Sustained VT/VF indicates a further invasive approach by electrophysiological testing, coronary angiography, or ICD implantation.

However, SMART-MI also evaluates the impact of telemonitoring on clinical end points including death, stroke, and unplanned hospitalizations. For this purpose, arrhythmic events are transmitted on a daily base to an ICM core laboratory. Treatment paths have been developed in line with current guidelines for different kinds of arrhythmias and include diagnostic workup as well as therapeutic interventions. Such interventions may include optimization of medical therapy, initiation of oral anticoagulation, revascularization, ablation, and device implantation.

There are several limitations of the SMART-MI study that should be recognized. First, the maximum age of patients included is 80 years. Therefore, the results will not allow extrapolation to older post-MI patients. Second, the study is restricted to patients in sinus rhythm. Third, data on stability of DC and PRD measurements are lacking. To address this issue, we will reevaluate DC and PRD after 12 and 24 months. Fourth, the primary end point is a diagnostic end point. Although clinical outcomes are included in the secondary end point, the study is not powered for these analyses. Finally, treatment recommendations are based on current guidelines.

However, for certain arrhythmias such as asymptomatic atrial fibrillation or nonsustained VT, no clear guideline recommendations exist.

In conclusion, SMART-MI seeks to evaluate the usefulness of ICMs for detection of serious arrhythmic events in high-risk postinfarction patients with LVEF 35%-50% and evidence of cardiac autonomic dysfunction. SMART-MI will provide information about the prognostic relevance of detected arrhythmias and their temporal relationships to clinical events. Thus, the findings of SMART-MI will provide the basis for developing preventive strategies in this important patient group.

Conflict of interest

None of the authors have any conflict of interest. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

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Stent Polymers
Do They Make a Difference?

Konstantinos D. Rizas, MD; Julinda Mehilli, MD

Abstract—The necessity of polymers on drug-eluting stent (DES) platforms is dictated by the need of an adequate amount and optimal release kinetic of the antiproliferative drugs for achieving ideal DES performance. However, the chronic vessel wall inflammation related to permanent polymer persistence after the drug has been eluted might trigger late restenosis and stent thrombosis. Biodegradable polymers have the potential to avoid these adverse events. A variety of biodegradable polymer DES platforms have been clinically tested, showing equal outcomes with the standard-bearer permanent polymer DES within the first year of implantation. At longer-term follow-up, promising lower rates of stent thrombosis have been observed with the early generation biodegradable polymer DES platforms compared to first-generation DES. Whether this safety benefit still persists with newer biodegradable polymer DES generations against second-generation permanent polymer DES needs to be explored. **(*Circ Cardiovasc Interv*. 2016;9:e002943. DOI: 10.1161/CIRCINTERVENTIONS.115.002943.)**

Key Words: drug-eluting stents ■ follow-up studies ■ percutaneous coronary intervention ■ polymers ■ thrombosis

With drug-eluting stent (DES) platforms representing the concept of combined mechanical stenosis repair and localized drug delivery, percutaneous coronary intervention became a pharmacomechanical therapy option for coronary artery disease. The concept of drug coating of metallic scaffolds is ≈20 years old and started with the aim to increase the hemocompatibility of metallic scaffolds.[1] In the era when plain balloon angioplasty was the default percutaneous coronary intervention option and the incidence of acute ischemic events was at double-digit levels, heparin-coated stents have been shown effective in reducing stent thrombosis without any measurable effect on neointimal formation.[1,2] Development of heparin-coated stent platforms revealed the difficulties of producing a stable system able to deliver the needed amount of the active drug without compromising its chemical sequence. Different from physical adsorption and ionic binding techniques, copolymerization of heparin with a variety of polymers provided stable heparin binding on the stent surface.[3] This experience, among others, explained later in this review, served as a prerequisite for development of various DES platforms, which have revolutionized the percutaneous coronary intervention field.

Advantages With Nonbiodegradable Polymers

Success of DES platforms in reduction of neointimal hyperplasia depends on the amount and kinetics of drug released. The experience with various formulations of polymer-free paclitaxel-eluting stents[4,5] or polymer-free sirolimus-eluting stents (SESs)[6] loaded with different increasing drug amounts demonstrated the importance of the drug amount for effective inhibition of neointima proliferation at an acceptable safety profile. The amount of drug loading through direct drug adsorption on the metallic surface is limited. Furthermore, most of the drugs are not able to adhere appropriately on the stent surface to insure controlled release. Therefore, polymer coating has become a key component of different DES platforms. Various permanent (biostable) and biodegradable polymers (BPs) have been used on DES platforms (Table 1).[7–12] Polymers selected to be used as a drug carrier should share following features: be biocompatible; do not interact with the active drug; provide a platform for appropriate drug-eluting kinetics; behave biologically inert after the drug has been completely eluted, and be mechanically stable at long-term in the dynamics of coronary circulation milieu.

Poly-(*n*)-butyl methacrylate, an inert synthetic polymer, has been used as a drug carrier on the first-generation SES, Cypher stent (Cordis, Johnson & Johnson, Miami Lakes, FL). The complex drug–polymer matrix on the Cypher stent (Table 2) allows a slow sirolimus release resulting in elution of 80% of drug within the first 30 days after DES implantation.[3] In contrast to this, the drug–polymer system of the paclitaxel-eluting stent, Taxus stent (Boston Scientific Corp, Natick, MA), based on a single layer of Translute (Table 1) polymer allows the release of <10% of the paclitaxel within 10 days after DES implantation, whereas the remaining drug persists within the polymer lifelong.[3] There is a large body

Received October 19, 2015; accepted March 15, 2016.

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Table 1. Characteristics of Polymers Used for Coronary Stent Coating

Polymer	Structure	Special Features	Suitability for Stent Coating
Nonbiodegradable polymers			
Parylene C	Highly crystalline material deriving from poly-para-xylylene monomer after substitution of a chlorine atom for one of the aromatic hydrogens	Vapor-phase deposition forming a structural continuous film as thin as 0.0001 inch, providing true pinhole-free conformal insulation, which makes it the material of choice for first-layer device coating	Excellent barrier properties attributable to lower permeability to moisture and corrosive gases, such as nitrogen, oxygen, and carbon dioxide while retaining excellent electric properties
PBMA[7]	Transparent liquid with high hydrophobicity and durability at molecular weight (200 000–320 000 Daltons)	Biocompatible with slow drug-release kinetics	Coating entirely made off PBMA develops cracks in the presence of significant concentrations of drug. Therefore, PBMA and PEVA polymers are used as a mixture for stent coating
PEVA[7]	PEVA copolymer consistency depends on the % of vinyl acetate with increasingly high durability at higher percentages	Rapid drug-release kinetics (50% within 24 h)	Coatings entirely made off PEVA are less durable but flexible and release drugs relatively rapidly. Therefore, PBMA and PEVA polymers are used as a mixture for stent coating
SIBS[8]	The triblock SIBS polymer is a self-assembled physically cross-linked polyisobutylene. It is a thermoplastic elastomer with physical properties that overlap silicone rubber and polyurethane, susceptible to stress cracking in the presence of organic solvents with poor creep properties	Soluble in various nonpolar solvents, thus can be spray coated. Poor gas permeability which renders it more cumbersome to sterilize with ethylene oxide and not γ-ray sterilizable	Oxidatively, hydrolytically, and enzymatically stable over its lifespan in the body with a relatively low foreign-body reaction
PC[9]	Thermoset, water-swellable methacrylate polymer comprised of 4 monomers: (1) 2-methacryloyloxyethyl PC monomer; (2) lauryl methacrylate; and (3) 2-hydroxypropyl-methycrylate both attenuate hydrophilicity; whereas (4) trimethoxysilylpropyl methacrylate is a silane crosslinker, which determines the mechanical proprieties of PC polymer	The zwitterionic PC group in the 2-methacryloyloxyethyl PC monomer provides the hydrophilic and biomimetic surface similar to the PC head group in the cell membrane of erythrocytes	Lower thrombogenecity
PVDF-HFP[9]	Semicrystalline fluorinated copolymer of vinylidene fluoride and hexafluoropropylene monomers. Its backbone is composed entirely of saturated carbon–carbon single bonds, which are >50% fluorinated resulting in polymer hydrophobicity	High elasticity and fatigue resistance attributable to low glass transition temperature of –29°C and semicrystallinity	Resistant to hydrolytic, oxidative, or enzymatic cleavage because of the lack of any reactive or enzymatic sensitive groups
BioLinks[10]	Mixture of 3 polymers: the C10 polymer is comprised of hydrophobic *n*-butyl methacrylate, which binds the drug and a small amount of vinyl acetate. The C19 polymer is synthesized from a mixture of hydrophobic *n*-hexyl methacrylate and hydrophilic *N*-vinyl pyrrolidone and vinyl acetate monomers to provide enhanced biocompatibility. Polyvinyl pyrrolidone is a medical grade hydrophilic polymer	Polymers self-orientation resulting in a surface substantially hydrophilic, whereas the core remains substantially hydrophobic	Enhanced biocompatibility
Biodegradable copolymers			
PDLLA[11]	PLA polymer exists in an optically active stereoregular form (semicrystalline L-PLA) and in an optically inactive racemic form, PDLLA	Fully biodegradable by bulk hydrolysis at uniform rate throughout the polymer matrix. During bioresorption, long chains are progressively shortened through cleavage of its backbone ester linkages. The PLA enters the tricarboxylic acid cycle and is eliminated from body as carbon dioxide and water	Homogeneous dispersion of the drug within the polymer matrix because of its amorphous structure

(*Continued*)

Table 1. Continued

Polymer	Structure	Special Features	Suitability for Stent Coating
PLGA[11]	PGA is highly crystalline and less hydrophobic compared with PLA because of the lack of the methyl site. The type and ratio of the individual PLA and PGA monomers determine PLGA crystallinity	Fully biodegradable with PLA degradation through tricarboxylic acid cycle, whereas PGA is either excreted unchanged in the kidney or metabolized through tricarboxylic cycle	Adjustable mechanical strength and biodegradation rate because of distinct ability of polymer crystallinity modification
PLEC[12]	PLEC is analiphatic semicrystalline polyester produced by ring-opening polymerization of a lactone	Particularly miscible with a variety of polymers. Progressive increase of cristallinity when molecular weight and annealing are decreased, which reduces polymer permeability	Low biodegradability by slow hydrolysis. Changeable drug-eluting process during biodegradation, at start, predominate drug dissolution and later, drug diffusion

PC indicates phosphorylcholine; PBMA, poly-*n*-butyl methacrylate; PDLLA, poly(D,L)-lactic acid; PEVA, polyethylene-co-vinyl acetate; PGA, polyglycolide acid; PLA, polylactide acid; PLEC, poly(L-lactide–co-ε-caprolactone); PLGA, poly(D,L-lactide-co-glycolide); PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene); and SIBS, poly(styrene-block-isobutylene-block-styrene).

of scientific evidence demonstrating the superiority of SES compared with paclitaxel-eluting stent on the antirestenotic efficacy and safety,[13] thus identifying the limus-family drugs as the most appropriate and effective for DES coating.

The importance of the type of the polymer became evident during the development of newer DES platforms. Coating with a polymer composed of methacryloyloxyethyl lauryl methacrylate and a synthetic form of phosphorylcholine has been used in the first version of the zotarolimus-eluting stent (ZES). Phosphorylcholine is the major component of the outer layer of the cell membrane, and coating on metallic scaffolds has been shown to increase their biocompatibility and hemocompatibility.[14] Two DES platforms based on the phosphorylcholine polymer coating have been clinically tested: Endeavor ZES (Medtronic Cardio Vascular Inc, Santa Rosa, CA) and ZoMaxx ZES (Abbott Vascular, Santa Clara, CA). The main difference between them consists on drug-release kinetics. After implantation of Endeavor ZES, 98% of zotarolimus is eluted within 14 days, whereas after implantation of ZoMaxx ZES, 90% of zotarolimus is released within 30 days.[15] In large randomized trials, the fast drug-release formulation of ZES has been shown inferior to the first-generation SES on antirestenotic efficacy.[16,17] Therefore, the manufacturer modified the polymer carrier of Endeavor stent (BioLinx tripolymer; Table 1) without changing the other components of the ZES platform. Waseda et al[15] investigated the effect of polymer formulations on neointimal proliferation after ZES implantation. At follow-up, intravascular ultrasound-determined percent neointimal obstruction was significantly lower in Resolute ZES (BioLinx polymer—slow drug-release kinetic), compared with Endeavor and ZoMaxx ZES (phosphorylcholine polymer—fast and intermediate drug-release kinetic): 3.7±4.0, 17.5±10.1, and 14.6±8.1, respectively.[15] Furthermore, we reported significantly lower angiographic in-stent late lumen loss (LLL) with Resolute ZES (0.29±0.56 mm) compared with Endeavor ZES (0.58±0.55 mm).[18] The intracoronary imaging and angiographic data are supported by the clinical outcomes reported in a large meta-analysis of 12 randomized trials—Resolute ZES was associated with 60% reduction of ischemia-driven target lesion revascularization and ≈50% reduction of ischemia-driven target vessel revascularization compared with Endeavor ZES.[19] This experience highlights the key role of polymer on DES platforms as an essential element for drug-release control, determining the final clinical performance of DES.

Currently, the everolimus-eluting stent (EES), Xience stent (Abbott Vascular, Santa Clara, CA), is considered as the standard-bearer among the DES platforms. Different from the first-generation DES, EES has a thin-strut cobalt-chromium backbone of 81 μm (instead of 130–140 μm) and has a novel polymeric drug carrier, the noninflammatory ultrapure fluorinated copolymer.[20] Large randomized trials and different network meta-analyses demonstrated particularly increased safety with EES platform compared with both bare metal stent and other DES platforms.[21–23] The most intriguing finding is the observed 80% reduction of early stent thrombosis with EES compared with bare metal stent.[22] In ex vivo shunt models and animal studies, less platelet aggregation and less inflammatory cell attachment, as well as earlier endothelialization, have been observed with EES compared with other thick- or thin-strut DES or bare metal stents.[24–26] Added to the clinical evidence of lower acute stent thrombosis with EES, the accumulated evidence strongly suggests acute thromboresistance of EES platforms related to the presence of permanent fluorocopolymer coating.

Disadvantages With Non-BPs

The success of first-generation DES was shadowed by the observed increased risk of late stent thrombosis and late catch-up restenosis.[13,27] Alongside drug toxicity and hypersensitivity, the permanent persistence of the durable polymer was identified as trigger of impaired arterial healing.[28] In animal studies, durable polymers on first-generation SES and paclitaxel-eluting stent provoke chronic inflammation, which triggers impaired arterial healing.[29,30] Furthermore, although considered biostable, a degradation of the poly-(*n*)-butyl methacrylate polymer from the stent surface at long-term has been reported.[31] The released methacrylate acid induces vascular smooth muscle cell apoptosis, which might delay maturation and normalization of endothelium function, consequently

Table 2. Characteristics of CE-Approved Polymer-Based DES Tested in Randomized Controlled Trials

Stent	Bare-Stent Material	Polymer	Polymer Degradation	Drug	Drug-Eluting Time
BioMatrix Flex	316S SS	PDLLA	6–9 mo	Biolimus A9, 15.6 μg/mm	40% at time of PCI; 60% in 6–9 mo
Combo	316 L SS	PDLLA and PLGA and coating with anti-CD34		Sirolimus	
Cypher	316 L SS	1st coat: parylene C; 2nd and 3rd top coat: PEVA and PBMA	No	Sirolimus, 180 μg/cm^2	80% in 1 mo
DESyne Nx	Co-Cr	PBMA	No	Novolimus, 5 μg/mm	4–6 wk
Endeavor	Co-Cr	PC with base coat	No	Zotarolimus, 10 μg/mm	98% in 0.5 mo
Firehawk	Co-Cr with abluminal grooves	PLA	6–9 mo	Sirolimus, 3 μg/mm	75% in 1 mo
MiStent	Co-Cr	PLGA	3 mo	Crystalline sirolimus, 2.44 μg/mm^2	9 mo
Nobori	316S SS	PDLLA	12 mo	Biolimus A9, 15.6 μg/mm	40% at time of PCI; 60% in 6–9 mo
Orsiro	Co-Cr covered with an amorphous silicon-carbide layer	PLLA	14 mo	Sirolimus, 1.4 μg/mm^2	12 mo
Promus element	PI-Cr	PBMA and PVDF-HFP	No	Everolimus, 100 μg/cm^2	80% in 1 mo
Resolute	Co-Cr	BioLinks	No	Zotarolimus, 10 μg/mm	85% in 2 mo; 15% in 6 mo
Synergy	PI-Cr	PDLLA	4 mo	Everolimus, 100 μg/cm^2	3 mo
Yukon choice PC	316 L SS microporous stent	PDLLA	2–3 mo	Sirolimus, 4.8 μg/mm^2	95% in 1 mo
Ultimaster	Co-Cr	PDLLA and PLEC	4 mo	Sirolimus, 3.9 μg/mm	30% at the time of PCI; the rest released to polymer bioabsorption
TAXUS Express	326 L SS	SIBS	No	Paclitaxel	10% in 0.5 mo; 90% is in polymer forever
Xience	Co-Cr	PBMA and PVDF-HFP	No	Everolimus, 100 μg/cm^2	80% in 1 mo

CE indicates Conformité Europeenne; CoCr, cobalt-chromium; DES, drug-eluting stent; PC, phosphorylcholine; PCI, percutaneous coronary intervention; PBMA, poly-*n*-butyl methacrylate; PDLLA, poly(D,L)-lactic acid; PEVA, polyethylene-co-vinyl acetate; PGA, polyglycolide acid; PICr, platinum-chromium; PLA, polylactide acid; PLEC, poly(L-lactide–co-ε-caprolactone); PLGA, poly(D,L-lactide-co-glycolide); PLLA, poly-L lactic acid; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene); SIBS, poly(styrene-block-isobutylene-block-styrene); and SS, stainless steel.

impairing the vascular healing process.[31] Poor stent-strut coverage related to delayed arterial healing has been identified as the pathological substrate of late and very late stent thrombosis after the implantation of first-generation DES.[28] Although a lower prevalence of uncovered stent struts with second-generation thin-strut DES compared with first-generation DES has been observed, the reported frequency of neoatherosclerosis remained similar with both DES generations.[32,33]

In-stent neoatheroslerosis has been observed after implantation of intracoronary metallic scaffolds with or without drug coating. However, it occurs much earlier and more frequently after DES implantation. Unstable neoatherosclerosis has been identified within 2 years after first-generation DES implantation and within 5 years after bare metal stent implantation.[33,34] Its development has been speculated to be based on impaired endothelialization of the stented segment with polymer-induced chronic inflammation as one of the triggers of this process.[33] Previous studies have demonstrated a chronic inflammatory reaction with an acute component and a persistent foreign-body response with different types of polymers, which are currently being used on DES platforms.[29,35] Although this has been demonstrated even for poly-lactic-co-glycolic acid BPs, Lincoff et al[35] demonstrated less inflammatory response after implantation of stents using a high-molecular weight form of poly-lactic-co-glycolic acid. Furthermore, BPs are only temporary on the stent surface having the potential of less or no chronic inflammation of the stented vessel wall after they completely erode.

BP-Based DESs

Development of BP-DES platforms is the obvious result of the accumulated evidence with earlier DES generations and increased knowledge about the histopathologic substrate behind adverse events after DES implantation. Several randomized trials comparing BP-DES with permanent polymer DES (PP-DES) platforms have been performed (Table 3).[36–56] In the Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis (ISAR-TEST 3) and 3

Table 3. Randomized Trials Comparing BP-DES vs PP-Limus-Eluting Stent

Study	Patients' Number	BP-DES Type	PP-DES Type	Population	Primary End Point
BASKET-PROVE II[36]*	1530	BP-BES	PP-EES	De novo native artery lesions; vessel size ≥3 mm, without left main lesions, without cardiogenic shock or planned surgery <1 y, and without increased bleeding risk	Composite of cardiac death, nonfatal MI, or clinically driven non-MI–related TVR within 2 y
BIFLOW II[37]	452	BP-SES	PP-EES	Stable or unstable CAD, silent ischemia, or clinical evidence of myocardial ischemia; de novo native coronary artery lesions <26 mm in length; vessel size 2.25–4.0 mm; without MI <72 h; without left main artery or 3-vessel disease; with LVEF >30%	In-stent LLL at 9-mo repeat angiogram
BIOSCIENCE[38]	2119	BP-SES	PP-EES	Stable CAD or ACS, with both de novo or restenotic lesions in native coronary arteries or bypass grafts	TLF at 1 y
CENTURY II[39]	1816	BP-SES	PP-EES	Stable or unstable CAD; de novo native artery lesion; vessel size 2.5–4.0 mm; without MI <48 h; without PCI <30 d; without bifurcation or left main lesions or >2 vessels to be treated	Freedom from TLF at 9 mo
COMPARE II[40,41]	2707	BP-BES	PP-EES	De novo native coronary artery lesions; vessel size 2.0–4.0 mm; life expectancy ≥5 y; without planed major surgery ≤30 d; without cardiogenic shock or previous DES implantation ≤1 y	Composite of cardiac death, nonfatal MI, and clinically driven TVR within 12 mo
DESSOLVE II[42,43]	184	BP-SES	PP-ZES	Stable angina pectoris; single de novo type A/B1/B2 lesions; vessel size, 2.5–3.5 mm; stenosis length <30 mm	In-stent LLL at 9-mo repeat angiogram
EVOLVE[44]	291	BP-EES	PP-EES	Stable or unstable CAD, silent ischemia, or clinical evidence of myocardial ischemia; de novo native coronary artery lesion ≤28 mm; vessel size, 2.5–3.5 mm; coronary TIMI flow >1; without recent MI; without bifurcation lesions	TLF at 30 d
EVOLVE II[45]	1684	BP-EES	PP-EES	Stable or unstable CAD, silent ischemia, or clinical evidence of myocardial ischemia; ≤3 de novo native coronary artery lesion ≤34 mm in length; vessel size, 2.25–4.0 mm; without recent ST-segment–elevation MI; without left main disease or chronic total occlusions.	TLF at 1 y
ISAR-TEST 3[46]*	404	BP-SES	PP-SES	Ischemic symptoms or evidence of myocardial ischemia with at least 1 de novo stenosis in native coronary vessels	In-stent LLL at 6–8 mo repeat angiogram
ISAR-TEST 4[47,48]	2603	BP-SES	PP-EES; PP-SES	Ischemic symptoms or evidence of myocardial ischemia with at least 1 de novo stenosis native coronary vessels	TLF at 1 y
LEADERS[49,50]	1707	BP-BES	PP-SES	Stable CAD or ACS with at least 1 lesion suitable for coronary stent implantation; vessel size, 2.25–3.5 mm	Composite of cardiac death, MI, and clinically indicated TVR at 9 mo
NEXT[51,52]	3241	BP-BES	PP-EES	Patient eligible for PCI with DES willing to comply with follow-up for ≤3 y	TLR at 1 y; death or MI within 3 y
Nobori Japan[53]	335	BP-BES	PP-SES	Stable or unstable ischemic heart disease; de novo lesions in ≤2 native coronary vessel disease; vessel size, 2.5–3.5 mm; ≤30 mm in length; with LVEF >30%; without MI <72 h; without planed surgery or PCI after index PCI; without bifurcation, left main, or ostial lesions; without thrombotic lesions	Freedom from cardiac death, MI, and TVR at 9 mo
SORT OUT V[54]	2464	BP-BES	PP-SES	Chronic stable CAD or ACS; at least 1 de novo lesion in native coronary arteries eligible for PCI	Composite of cardiac death, MI definite ST, and clinically driven TVR at 9 mo
SORT OUT VI[55]	2999	BP-BES	PP-ZES	Stable CAD or ACS, including MI with or without ST-segment–elevation; at least 1 coronary lesion eligible for PCI; vessel size, 2.25–4.0 mm	Composite of cardiac death, MI not clearly attributable to a nontarget lesion, clinically indicated TLR at 1 y
TARGET I[56]	458	BP-SES	PP-EES	Stable CAD with single de novo coronary lesion; vessel size, 2.5–4.0 mm; length, <24 mm; without bifurcation, left main or chronic occlusion lesions	In-stent LLL at 9 mo repeat angiogram

ACS indicates acute coronary syndromes; BASKET-PROVE II, Safety and Efficacy Study Comparing 3 New Types of Coronary Stents; BIOFLOW II, Study of the Orsiro Drug Eluting Stent System; BIOSCIENCE, Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents; BP-BES, biodegradable polymer biolimus-eluting stent; BP-EES, biodegradable polymer everolimus-eluting stent; BP-SES, biodegradable polymer sirolimus-eluting stent; CAD, coronary artery disease; CENTURY II, Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease; COMPARE II, Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent; DES, drug-eluting stents; DESSOLVE II, Clinical Investigation of the MiStent DES in Coronary Artery Disease; EVOLVE II, Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s); ISAR-TEST 3, Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis; ISAR-TEST 4, 3 Limus Agent Eluting Stents With Different Polymer Coating; LEADERS, Limus Eluted From a Durable Versus Erodable Stent Coating; LLL, late lumen loss; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NEXT, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial; PCI, percutaneous coronary intervention; PP-DES, permanent polymer drug-eluting stents; PP-EES, permanent polymer everolimus-eluting stent; PP-SES, permanent polymer sirolimus-eluting stent; PP-ZES, permanent polymer zotarolimus-eluting stent; SORT-OUT V, Randomised Clinical Comparative Study of the Nobori and the Cypher Stent; SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity; ST, stent thrombosis; TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V; TIMI, Thrombolysis in Myocardial Infarction; TLF, target lesion failure; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*Only patients receiving polymer-based drug-eluting stents.

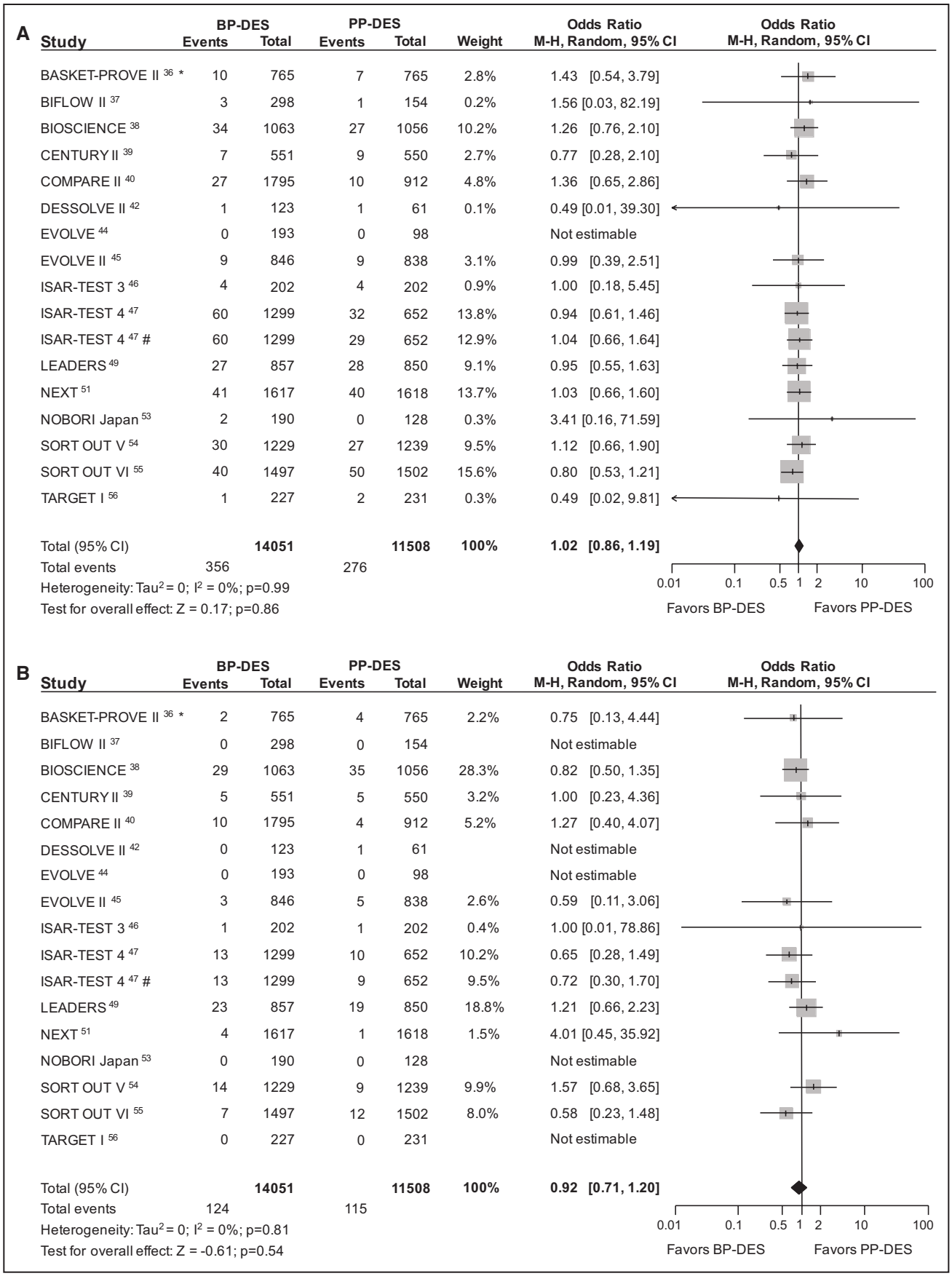

Figure 1. (*Continued*)

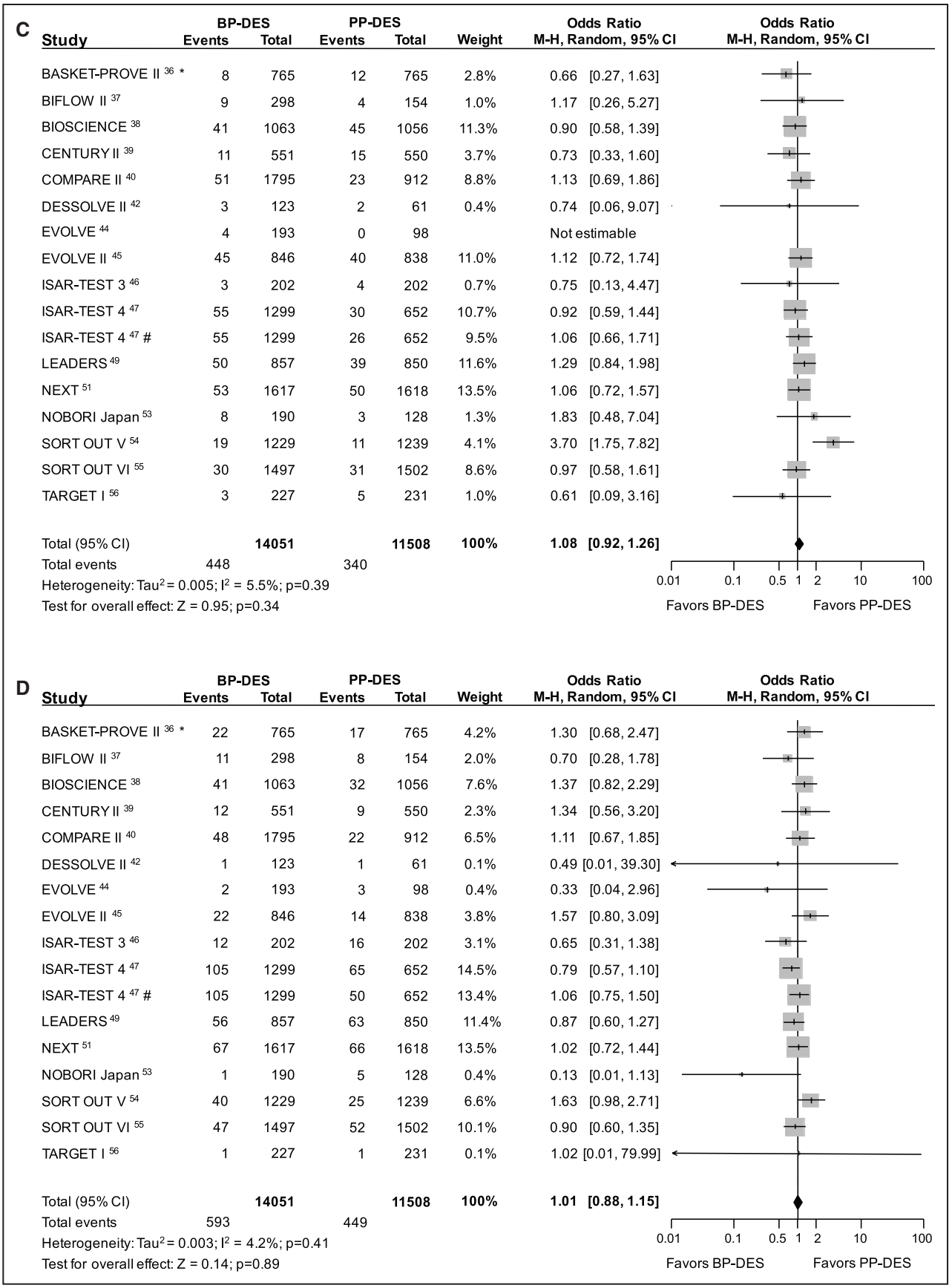

Figure 1 Continued. One-year death (**A**), 1-year definite/probable stent thrombosis (**B**), 1-year myocardial infarction (**C**), and 1-year target lesion revascularization (**D**). BASKET-PROVE II indicates Safety and Efficacy Study Comparing 3 New Types of Coronary Stents; BIO-FLOW II, Study of the Orsiro Drug Eluting Stent System; BIOSCIENCE, Sirolimus-Eluting Stents With Biodegradable Polymer (*Continued*)

Figure 1 Continued. Versus an Everolimus-Eluting Stents; BP-DES, biodegradable polymer drug-eluting stent; CENTURY II, Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease; CI, confidence interval; COMPARE II, Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent; DESSOLVE II, Clinical Investigation of the MiStent DES in Coronary Artery Disease; EVOLVE II, Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s); ISAR-TEST 3, Rapamycin-Eluting Stents With Different Polymer Coating to Reduce Restenosis; ISAR-TEST 4, 3 Limus Agent Eluting Stents With Different Polymer Coating; LEADERS, Limus Eluted From a Durable Versus Erodable Stent Coating; M-H, Mantel-Haenszel; NEXT, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial; PP-DES, permanent polymer drug-eluting stent; SORT-OUT V, Randomised Clinical Comparative Study of the Nobori and the Cypher Stent; SORT OUT VI, Randomized Clinical Comparison of Biomatrix Flex and Resolute Integrity; and TARGET I, Randomized MicroPort's Firehawk DES Versus Xience V.

Limus Agent Eluting Stents With Different Polymer Coating (ISAR-TEST 4), we compared sirolimus-eluting BP-DES to standard-bearer permanent polymer–based SES and EES. In-stent LLL at 6 to 8 months of angiography was 0.17±0.45 mm with BP-SES and comparable to PP-SES (0.23±0.46 mm).[46,47] Lack of difference in the 5-year rates of target lesion revascularization observed with BP-SES (13.9%), PP-EES (12.6%), and PP-SES (15.6%) confirmed the early angiographic findings.[48]

The Limus Eluted From a Durable Versus Erodable Stent Coating (LEADERS) investigators who randomly compared BP-BES (Biomatrix, Biosensors) with PP-SES (Cypher) reported similar rates of the composite end point of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization within 9 months of DES implantation (9.2% with BP-BES versus 10.5% with PP-SES; relative risk, 0.88; 95% confidence interval [CI], 0.64–1.19; $P_{\text{noninferiority}}$=0.003).[49] While at 5-year follow-up the cumulative

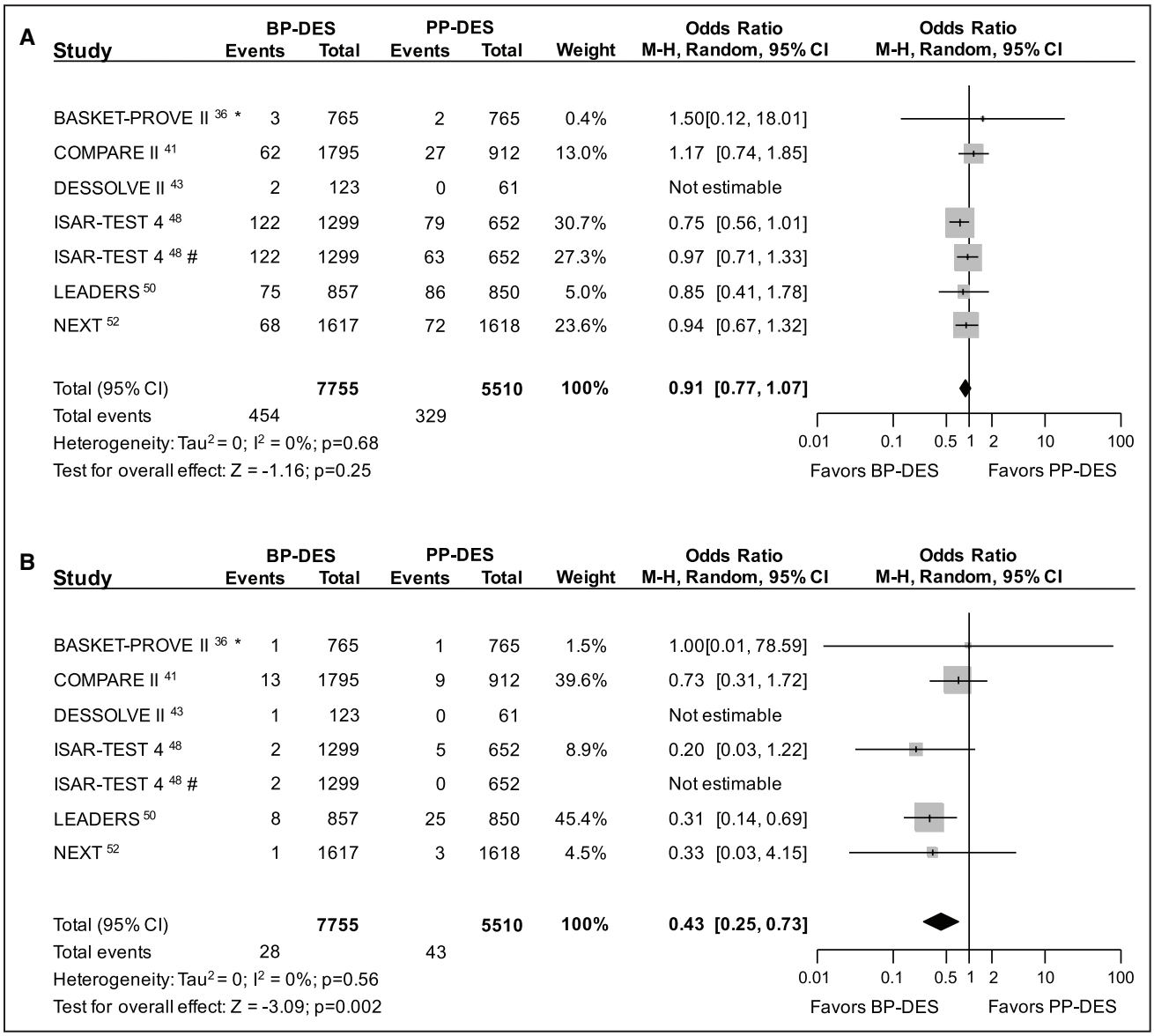

Figure 2. Longer-term death (**A**), longer-term definite/probable stent thrombosis (**B**), longer-term myocardial infarction (**C**), and longer-term target lesion revascularization (**D**). (*Continued*)

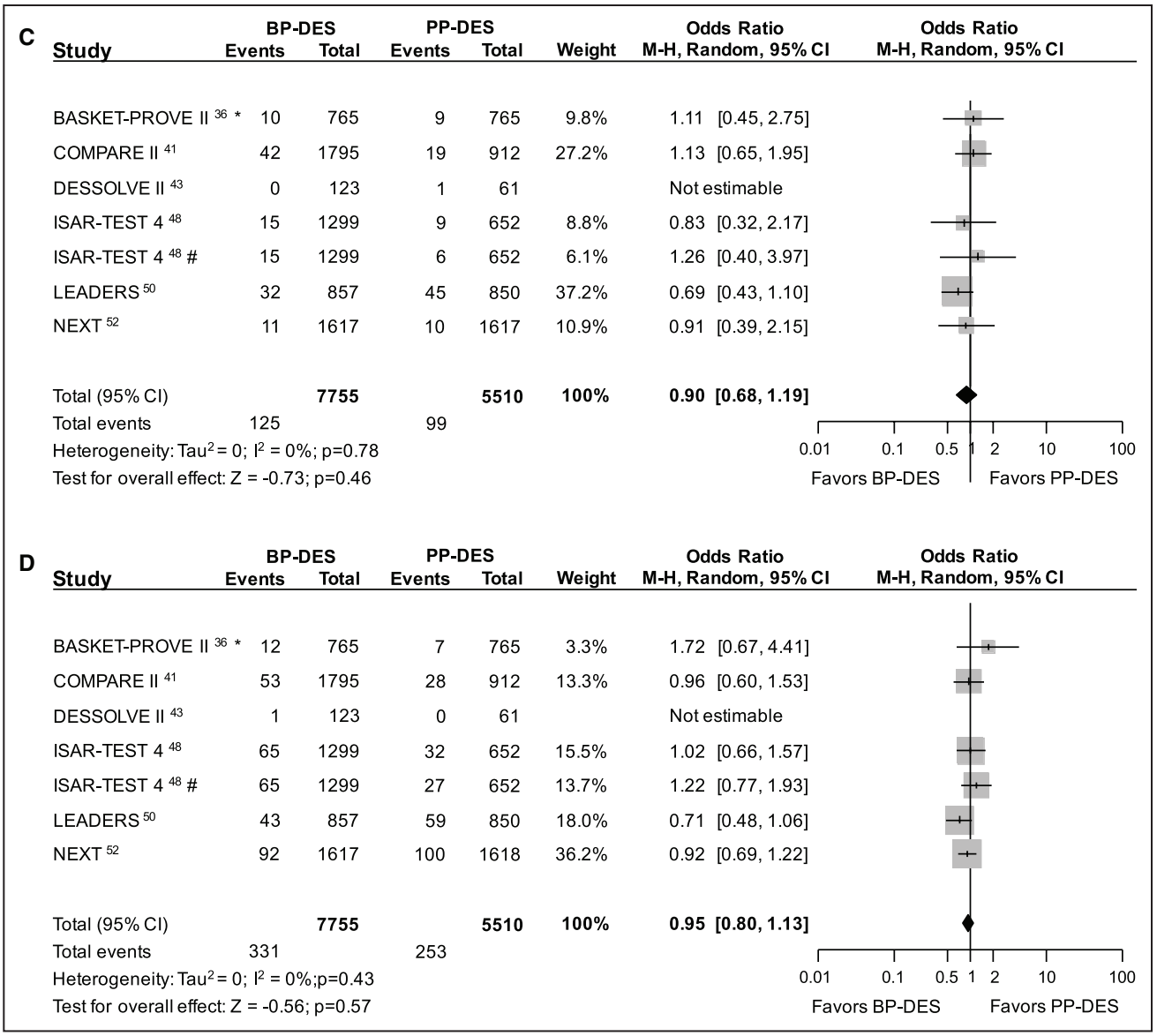

Figure 2 Continued. *Data available for BASKET-PROVE II[36] trial are cardiac death, nonfatal myocardial infarction, and target vessel revascularization. #ISAR-TEST 4[47,48] the comparator permanent polymer drug-eluting stent (PP-DES) is everolimus-eluting stent, Xience stent. §Data available for DESOLVE trials[42,43] were clinically driven target lesion revascularization. BASKET-PROVE II indicates Safety and Efficacy Study Comparing 3 New Types of Coronary Stents; BP-DES, biodegradable polymer drug-eluting stent; CI, confidence interval; COMPARE II, Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent; DESSOLVE II, Clinical Investigation of the MiStent DES in Coronary Artery Disease; ISAR-TEST 4, 3 Limus Agent Eluting Stents With Different Polymer Coating; LEADERS, Limus Eluted From a Durable Versus Erodable Stent Coating; M-H, Mantel-Haenszel; NEXT, Nobori Biolimus-Eluting Versus Xience/Promus Everolimus-Eluting Stent Trial; and PP-DES, permanent polymer drug-eluting stent.

incidence of primary end point was numerically lower with BP-BES (22.3%) compared with PP-SES, 26.1%, relative risk 0.83, 95% CI, 0.68 to 1.02; $P_{\text{noninferiority}}<0.001$.[50]

A limitation of both first-generation PP-DES and BP-BES (Biomatrix/Nobori) is their thick-strut stainless steel metallic backbone, which by itself is associated with higher risk of restenosis and might serve as a substrate for increased thrombogenicity.[25,57] However, in a porcine coronary model, thick-strut BP-BES revealed less inflammation and foreign-body immunoreaction than thin-strut PP-EES.[58] In the Test Safety of Biodegradable and Permanent Limus-Eluting Stents Assessed by Optical Coherence Tomography (TEST-6-OCT) trial, thick-strut BP-BES stent showed similar stent coverage and vascular healing response with thin-strut PP-EES ≤9 months after implantation.[59] The results of the Comparison of the Everolimus Eluting With the Biolimus A9 Eluting Stent (COMPARE II) trial, in which patients randomly received thick-strut BP-BES or thin-strut fluoropolymer-based EES, the current standard-bearer among DESs, support the animal and intracoronary imaging data. At 12-month follow-up, the primary end point—composite of cardiac death, nonfatal myocardial infarction, and clinically indicated target vessel revascularization—occurred in 5.2% of BP-BES and in 4.8% of PP-EES patients (relative risk, 1.07; 95% CI, 0.75 to 1.52; $P_{\text{noninferiority}}<0.0001$).[40] Despite these findings, in comprehensive network meta-analyses, thin-strut PP-EES and PP-ZES are identified as currently the safest stent

platforms even in comparison with thick-strut BP-BES.[23,60] This highlights the fact that performance of DES depends on the optimal combination of all 3 DES components—drug, metallic scaffold design, and polymer.

Similar to PP-DES platforms, the BP-DES technology has evolved toward thinner metallic backbones. Five new thin-strut BP-DES platforms received recently the Conformité Europeenne approval. The BP-SES, Ultimaster (Terumo Corporation, Tokyo, Japan) stent consists of a cobalt-chromium thin-strut (80 μm) platform coated with sirolimus in a matrix with bioresorbable poly(D,L-lactide-co-caprolactone) polymer at a unique gradient coating design intended to reduce polymer cracking and delamination on the hinges of the stent. Findings from the optical coherence tomography substudy of the Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients With Coronary Artery Disease (CENTURY II) trial revealed comparable tissue coverage with both BP-SES and PP-EES stents (mean neointimal thickness at 9 months, 110±10 versus 93±9 μm; *P*=0.22 and % of uncovered stent struts, 1.02 versus 2.26; *P*=0.35, respectively).[61] In the CENTURY II trial, patients enrolled in 58 centers from Europe, Japan, and Korea were randomly assigned to treatment with either thin-strut BP-SES or thin-strut PP-EES. Primary end point survival free of target vessel failure (cardiac death, target vessel myocardial infarction, and clinically indicated target lesion revascularization) at 9 months was 95.6% with BP-SES and 95.1% with PP-EES ($P_{noninferiority}$<0.0001).[39]

In the Sirolimus-Eluting Stents With Biodegradable Polymer Versus an Everolimus-Eluting Stents (BIOSCIENCE) trial, 2119 patients were randomly assigned to treatment with BP-SES or PP-EES.[38] The BP-SES (Orsiro, Biotronik AG, Bülach, Switzerland) is a novel DES platform consisting of an ultrathin (60–80 μm) cobalt-chromium L605 backbone covered with amorphous silicon-carbide layer and biodegradable poly-L-lactic acid polymer. Primary end point 12-month target lesion failure was with both BP-SES and PP-EES (6.7%). target lesion revascularization rates were 4.0% with BP-SES and 3.1% with PP-EES (rate ratio, 1.30; 95% CI, 0.82–2.06; *P*=0.27), whereas the incidence of definite/probable stent thrombosis was numerically lower with BP-SES (2.8%) compared with P-EES (3.4%; rate ratio, 0.83; 95% CI, 0.50–1.35; *P*=0.45).[38] To highlight is the very low in-stent LLL observed with the ultrathin Orsiro stent (0.1 mm), which is also identical to the in-stent LLL observed with the BP-EES (Synergy stent; Boston Scientific Corp).[37,44] The Synergy stent consists of thin-strut platinum-chromium backbone (74–81 μm), a biodegradable poly(D,L-lactide-co-glycolide) and the everolimus drug. In the Assess the Synergy Stent System for the Treatment of Atherosclerotic Lesion(s) (EVOLVE II) trial, target lesion failure at 1 year was virtually identical with both BP-EES and PP-EES (Promus Element stents; Boston Scientific Corp)—6.7% versus 6.4% respectively ($P_{noninferiority}$=0.0003).[45] In the Randomized MicroPort's Firehawk DES Versus Xience V (TARGET I) trial, the Firehawk stent (86-μm cobalt-chromium with abluminal grooves filled with polylactide acid and sirolimus; Microport Medical, Shangai, China) was noninferior to PP-ESS on the primary end point 9-month in-stent LLL (0.13±0.24 versus 0.13±0.18 mm, respectively; $P_{noninferiority}$<0.001).[56]

Another concept is tested in the design of BP-SES (MiStent platform; Micell Technologies, Durham, NS). The special feature of this stent is the absorbable polymer matrix containing a crystalline form of sirolimus. In the DESOLVE II randomized trial, MiStent performed superior to the Endeavor stent on the primary end point (in-stent LLL, 0.27±0.46 mm with MiStent versus 0.58±0.41 mm with Endeavor stent).[42]

We pooled the data from 16 randomized controlled trials in which thick- or thin-strut BP-based DES were compared with PP-based limus-eluting stents to assess differences in efficacy and safety parameters between these platforms (Table 3). As expected and observed in previous meta-analyses,[62,63] no additional benefit with BP-DES compared with PP-DES was identified on the efficacy and safety end points ≤1-year follow-up (Figure 1A–1D). However, advantages of BP-DES platforms would be expected to emerge later in time when polymer has been degraded. For only 6 of these trials, follow-up data between 2 and 5 years were available.[36,41,43,48,50,52] At longer-term follow-up, a significantly lower risk of stent thrombosis was observed with BP-DES compared with PP-DES (odds ratio, 0.43; 95% CI, 0.25–0.73; Figure 2A–2D). Although promising, this finding should be interpreted with caution. First, the outcomes derive mostly from 4 large trials in which the comparator was more frequently thick-strut first-generation SES. Second, the number of patients considered might be still not large enough for evaluation of such rare events. Comprehensive network meta-analyses, including larger cohorts of patients, considering randomized and nonrandomized trials, and performing mixed treatment comparisons, have yielded contradictory results in this regard.[23,60] Finally, in everyday practice, thick-strut BP-DESs are being substituted by the newer thin- or ultrathin BP-DES platforms. Long-term data with the latest ones are still lacking.

Summary

The necessity of polymers on DES platforms is dictated by the need of an adequate amount and optimal release kinetic of the antiproliferative drugs for achieving ideal DES performance. With the use of BPs to control drug release, the polymer-induced vessel inflammation, which partially triggers development of neoatherosclerosis with its clinical consequences very late stent thrombosis and restenosis, is limited in time. Indeed, the current data demonstrate increased long-term safety with the early generation BP-DES platforms compared with first-generation PP-DES. The newer BP-DES generations perform noninferior to second-generation PP-DES within the first year after implantation. Whether this transforms in safety benefit at long-term needs to be investigated.

Disclosures

J. Mehilli received lecture fees from Abbott Vascular and Terumo. K.D. Rizas reports no conflicts.

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