Aus dem Institut für Medizinische Psychologie
Institut der Ludwig-Maximilians-Universität München
Vorstand: Prof. Martha Merrow, PhD

Suggestibility as well as Psychosocial and Physical Long-term Consequences in Patients with a History of Stress-induced Cardiomyopathy

Dissertation
zum Erwerb des Doktorgrades der Humanbiologie
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

Elisabeth Gertrud Mathilde Olliges

aus

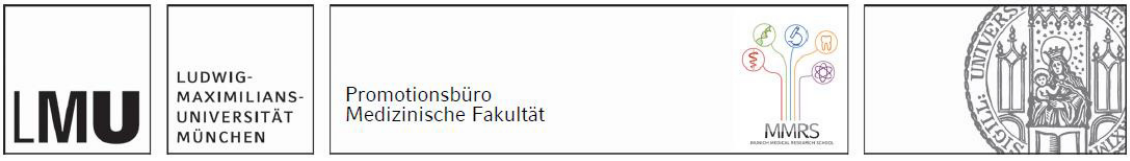
München

2021

Mit Genehmigung der Medizinischen Fakultät
der Universität München

Berichterstatter:	Prof. Dr. med. Karin Meißner
	_____
Mitberichterstatter:	PD Dr. med. Ute Wilbert-Lampen
	Prof. Dr. med. Andreas May
Mitbetreuung durch den promovierten Mitarbeiter:	----------
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	21.07.2021

Affidavit



Eidesstattliche Versicherung

Olliges, Elisabeth Gertrud Mathilde
Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Suggestibility as well as Psychosocial and Physical Long-term Consequences in Patients with a History of Stress-induced Cardiomyopathy

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 15.03.2021 — Elisabeth Gertrud Mathilde Olliges

Ort, Datum

Inhaltsverzeichnis

Abkürzungsverzeichnis

Abkürzung	*Bedeutung*
ACS	Acute Coronary Syndrome – Akutes Koronarsyndrom
ANS	Autonomic Nervous System – Autonomes Nervensystem
BP	Blood Pressure - Blutdruck
CNS	Central Nervous System – Zentrales Nervensystem
CVD	Cardiovascular Disease – Kardiovaskuläre Erkrankung
DBP	Diastolic Blood Pressure – Diastolischer Blutdruck
HR	Heart Rate - Herzrate
HRV	Heart Rate Variability - Herzratenvariabilität
i.v.	Intravenously - intravenös
M	Mean – Mittelwert
MI	Myocardial Infarction - Myokardinfarkt
SBP	Systolic Blood Pressure – Systolischer Blutdruck
TTC	Takotsubo Cardiomyopathy – Takotsubo Kardiomyopathie
TU	Technische Universität

Publikationsliste

Als Teil der vorgelegten Dissertation:

Olliges, E., Schneider, S., Schmidt, G., Sinnecker, D., Müller, A., Burgdorf, C., ... & Meissner, K. (2019). Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. Frontiers in psychiatry, 10, 549.

Olliges, E., Burgdorf, C., Ladwig, K. H., Moeller, C., Deftu-Kloes, D., Pohl, S., ... & Goetzmann, L. (2020). Psychosocial and physical long-term outcome in patients with a history of takotsubo cardiomyopathy or myocardial infarction-a multicentered case control study. Psychology, Health & Medicine, 1-15.

Weitere Publikationen

Aichner, S., Haile, A., Hoffmann, V., Olliges, E., Tschöp, M., & Meissner, K. (2019). The role of tactile stimulation for expectation, perceived treatment assignment and the placebo effect in an experimental nausea paradigm. Frontiers in Neuroscience, 13, 1212.

Meissner, K., Talsky, N., Olliges, E., Jacob, C., Salat, C., Braun, M., ... & Stoetzer, O. J. (2019). Individual Factors Contributing to Nausea in First-Time Chemotherapy Patients: A Prospective Cohort Study. Frontiers in pharmacology, 10, 410.

Goetzmann, L., Olliges, E., Ruettner, B., Meissner, K., Ladwig, K. H., Möller, C., ... & Steger, A. (2020). Adverse childhood experiences and the structure of personality in patients with takotsubo syndrome versus myocardial infarction. Heart and Mind, 4(1), 12.

Eggers, C., Olliges, E., Boeck, S., Kruger, S., Uhl, W., Meissner, K. (2020). Spiritual Meditation in addition to Conventional Medical Care in Patients with Advanced Pancreatic Cancer – a Pilot Study (under review).

1. Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Paper I

Die Konzeption der Studie, sowie die Erstellung des Ethikantrags habe ich selbstständig durchgeführt. Unterstützt wurde ich dabei von Prof. Dr. med. habil. Karin Meißner. Bei der Präsentation des Forschungsvorhabens vor der Ethikkommission der Technischen Universität (TU), München wurde ich unterstützt von Prof. Dr. med. habil. Karin Meißner, PP Dr. Joram Ronel und Prof. Dr. med. Georg Schmidt. Die Rekrutierung und Einbestellung der Probanden wurde von mir eigenständig durchgeführt. Die Interventionen wurden ebenfalls größtenteils von mir durchgeführt, unterstützt wurde ich dabei von den beiden ärztlichen Kollegen Dr. med. Simon Schneider und Dr. med. Daniel Sinnecker. Die Datenverarbeitung und Auswertung habe ich ebenfalls selbstständig durchgeführt, unter Mithilfe der Arbeitsgruppe *Biosignalverarbeitung* des Klinikums rechts der Isar, TU München um Prof. Dr. med. Georg Schmidt, die mir freundlicherweise das Messgerät (Finapres Medical Systems B.V.) zur Verfügung gestellt hat. Die statistische Auswertung habe ich selbstständig durchgeführt und das Manuskript eigenständig verfasst und beim entsprechenden Journal eingereicht, unterstützt wurde ich hierbei vor allem von Prof. Dr. med. habil. Karin Meißner, als auch von Teilen der Co-Autoren.

1.2 Beitrag zu Paper II

Ein positives Votum der Ethikkommission der TU München lag bereits vor, als ich das Studienprojekt übernommen habe. Die Datenerhebung an den Münchner Studienzentren (Deutsches Herzzentrum, TU, München und Medizinische Klinik und Poliklinik I, Klinikum rechts der Isar, TU München), als auch zu einem Großteil an den Standorten Lübeck (Medizinische Klinik II, Universitätsklinikum Schleswig-Holstein, Campus Lübeck) und Bad Segeberg (Bad Segeberger Kliniken) habe ich eigenständig durchgeführt. Die statistische Auswertung habe ich selbstständig durchgeführt. Das Manuskript habe ich eigenständig verfasst und beim entsprechenden Journal eingereicht. Unterstützt wurde ich dabei vor allem von Prof. Dr. med. habil. Karin Meißner als auch von weiteren Co-Autoren.

2. Introduction

2.1 Placebo and Nocebo Effects – Definitions of Terms

Current placebo research combines psychosocial aspects attributable to the therapeutic encounter and findings from neurobiology to demonstrate the interaction between body and mind (Frisaldi, Piedimonte, & Benedetti, 2015; Kaptchuk & Miller, 2015). Numerous scientific studies exposed significant placebo and nocebo effects in very different areas (Benedetti & Amanzio, 2011; Colloca & Miller, 2011; de la Fuente-Fernández et al., 2002; Hadamitzky, Sondermann, Benson, & Schedlowski, 2018). Recent findings suggest that psychosocial factors (e.g. empathetic care, the patient´s beliefs) and contextual factors (e.g. rituals, the method of administration) modify the biochemistry and neuronal circuits of the patient's brain (Benedetti & Amanzio, 2011; Kaptchuk & Miller, 2015). It could be shown that neuronal pathways activated through placebo and nocebo interventions can be similar to those activated by pharmacologically active drugs (Finniss, Kaptchuk, Miller, & Benedetti, 2010; Frisaldi et al., 2015; Grünbaum, 1994).

Although the number of publications on mechanisms attributed to placebo effects has increased rapidly in recent decades, there is no clear agreement on the definition of placebo and nocebo effects. Placebo and nocebo effects are understood as heterogenous phenomena and especially the definition of placebos as an inert material substance (e.g. a sugar pill) is increasingly questioned (Grünbaum, 1994; Jütte, 2013).

2.1.1 Placebo and Nocebo Effects in Cardiology

Initially, placebo and nocebo research mainly focused on parameters related to central nervous processes, especially on pain. Studies investigating placebo analgesia found that the reduction of pain is accompanied by a decrease in heart rate (HR) and heart rate variability (HRV) (Pollo, Vighetti, Rainero, & Benedetti, 2003). Accordingly, the expectancy of pain reduction seems to play a decisive role for the reduction of sympathetic activation (Aslaksen & Flaten, 2008; Wager et al., 2004).

Further on, subjective and objective parameters have increasingly been measured beyond the area of placebo analgesia and the underlying neurobiological

mechanisms are comprehensively investigated (Colloca, Lopiano, Benedetti, & Lanotte, 2005; Meissner et al., 2011). As a result, placebo and nocebo effects on functions related to an innervation of the autonomic nervous system (ANS), including cardiovascular functions (e.g. blood pressure (BP) and HR) are meanwhile increasingly examined.

However, Hróbjartsson and Gøtzsche investigated randomized controlled trials (RCTs) contrasting placebo treatments with no treatment and deduced that placebo effects, for instance on BP, are insignificant after controlling for factors that could have influenced the results, such as regression to the mean or habituation (Hróbjartsson & Gøtzsche, 2004). In contrast, there are several studies that demonstrated significant placebo and nocebo effects on heart and circulation related parameters; nonetheless they still hold many open questions.

Wilhelm and colleagues analyzed placebo groups within RCTs using beta-blocker to treat hypertension (Wilhelm, Winkler, Rief, & Doering, 2016). They found that almost half of the drug effect on diastolic blood pressure (DBP) and more than a third of the drug effect on systolic blood pressure (SBP) could be assigned to placebo effects, whereas placebo effects on HR could not be found.

The induction of expectations through verbal suggestions seems to be an important underlying mechanism. Benedetti and colleagues, among others, were able to show by means of open-hidden designs that the effect of Atropine and Beta-blocker on BP can be enhanced by verbal suggestions in the corresponding direction, compared to the pure pharmacological effect, without verbal explanations. The induced expectation enlarged the effect of the medication under both conditions (Benedetti et al., 2003).

Similar effects on SBP evoked by verbal suggestions could be shown even without an accompanying substance intake. Solely verbal suggestions in a therapeutic context seem to be sufficient to induce changes in BP. For instance, in an early study, hypertensive and normotensive subjects were either told their BP would rise, fall, or remain the same, respectively no information was given. SBP changes in the announced direction could be demonstrated. DBP and again HR were not affected in either group (Amigo, Cuesta, Fernández, & González, 1993).

Moreover, it could be demonstrated that verbal suggestions are able to induce effects on specific functions. Meissner and Ziep (2011) could show that SBP decreased as a response to specific verbal suggestions, while HR, HRV, situational anxiety and gastric activity remained unaltered. The results indicate that explicit verbal suggestions, involved in placebo or nocebo interventions, are able to specifically elicit the addressed changes (Meissner & Ziep, 2011).

However, effects on cardiac functions could not continuously proven to be significant in studies examining placebo and nocebo interventions. In an additional study by Zimmermann-Viehoff and colleagues, participants breathed in a placebo spray accompanied by the suggestion that it contained an effective drug to raise or lower BP, or that it was a placebo. No evidence was found that the explicit verbal suggestions throughout the placebo interventions affected BP in healthy subjects, despite of a successful induction of expectations (Zimmermann-Viehoff et al., 2013).

Hence, study results focusing on placebo effects on BP and HR are ambivalent, but several experimental studies indicate that at least on the short term, SBP can be affected by treatment-related expectations, induced through verbal suggestions.

2.2 Stress-induced Cardiomyopathy

Stress-induced cardiomyopathy, also called Tako-tsubo cardiomyopathy (TTC), is a very infrequent form of primary heart muscle diseases, mainly affecting postmenopausal women (Pilgrim & Wyss, 2008; Templin et al., 2015). Symptoms and signs are rather similar to those of a myocardial infarction (MI) during the acute phase. However, vessels supplying the heart are usually unaffected, but the contraction of the heart muscle presents itself to be impaired (Ghadri, Ruschitzka, Lüscher, & Templin, 2014).

Despite extensive efforts, 30 years after the first description of TTC in Japan, knowledge of underlying mechanisms is still limited (Ghadri et al., 2014; Sato, 1990). It has been observed that the alterations of the heart muscle are often preceded by a stressful event. By means of the comprehensive *International Takotsubo Registry*, Templin and colleagues could detect that approximately 30% of TTC patients experienced either an emotional, physical or no trigger previous

to the ongoing of the disease (Templin et al., 2015). Therefore, an excessive sympathetic nervous system activation seems to play an important role in the pathophysiology of TTC.

Interestingly, first studies indicate an increased chance for mental impairments such as depressive or anxiety symptoms in TTC patients (Delmas et al., 2012; Mudd, Kapur, Champion, Schulman, & Wittstein, 2007; Summers, Lennon, & Prasad, 2010). By means of the *International Takotsubo Registry* the assumption of an increased prevalence of psychiatric diseases in TTC patients could further be substantiated (Templin et al., 2015). Nonetheless knowledge on psychosocial risk factors and comorbidities in TTC patients is still limited in contrast to the field of cardiovascular diseases (CVD) (Albus, Ladwig, & Herrmann-Lingen, 2014; Ladwig et al., 2013; Pedersen, Von Känel, Tully, & Denollet, 2017; von Känel, 2016)

Since there is a rapid decrease in symptomatology, such as a rapid normalization of the left ventricular ejection fraction, TTC is usually considered a comparable harmless and reversible disease (Burgdorf, Kurowski, Bonnemeier, Schunkert, & Radke, 2008; Sharkey et al., 2010). At the same time, mortality in TTC patients was described as comparable to that of patients after MI, and a substantially increased death rate was found in TTC patients contrasted to a control group of the same age and sex (Elesber et al., 2007; Redfors et al., 2015; Valbusa et al., 2008).

2.3 Psychosocial Risk-factors in Cardiology

The term *psychocardiology* focusses on psychosocial factors in the development, course and rehabilitation of cardiological diseases. This approach provides an alternative, highly diversified perspective and a multifactorial genesis of cardiological diseases. In this connection, particular importance is attached to the role of psychosocial risk-factors (Ladwig et al., 2013; Pedersen et al., 2017).

Although the results of large-scale studies are still inconclusive, there is robust evidence that psychosocial factors, especially related to depression, anxiety, anger/hostility, social isolation, chronic or acute stress and loneliness, can be considered as the most important risk-factors for CVD (Christensen et al., 2020;

Pedersen et al., 2017; von Känel, 2016). Further, adverse childhood events seem to be critical for the development of CVDs (Pierce et al., 2020).

These factors are either acting separately or accumulated in clusters and exert their influence at different stages of life course (Ben-Shlomo & Kuh, 2002). Pathophysiological mechanisms underlying the relationship between psychosocial risk-factors and cardiac events can be divided into direct pathophysiological mechanisms or pathways such as the ANS, neurocrine activation, inflammatory processes; or behaviour related mechanisms like a lack of adherence to medication intake, smoking, physical inactivity or malnutrition (Everson-Rose & Lewis, 2005).

3 Research Questions

Placebo effects have developed from an unintended “by-product” in clinical research to an important, interdisciplinary research subject investigating a broad variety of medical conditions (Colloca & Miller, 2011; Evers et al., 2018). In addition, placebo and nocebo effects play a significant role in everyday medical practice, since the overall effect of each therapeutic intervention is composed of a specific effect (e.g. due to the chemical composition of a drug) and unspecific effects, including placebo and nocebo effects. Nocebo effects are often reflected in negative by-effects, enhanced by a close examination of the corresponding package insert for example (Enck, Bingel, Schedlowski, & Rief, 2013; Evers et al., 2018). Simultaneously, placebo and nocebo effects on heart related parameter are still ambivalent, as described above.

The etiology of TTC and the underlying pathophysiological mechanisms still raise questions. There is also disagreement on how harmful a TCC should be considered. On the one hand, the disease is considered benign and reversible, for example, due to the rapid recovery of the ejection fraction and the initially altered form of the heart muscle. At the same time, studies show a similar death rate as patients after MI (Burgdorf et al., 2008; Elesber et al., 2007; Ghadri et al., 2018). Although initial studies show an accumulation of affective comorbidities, little is known about the physical and psychosocial long-term consequences of TTC (Mudd et al., 2007; Summers et al., 2010; Templin et al., 2015).

Against this background, the first study included in this dissertation examined alterations of cardiac functions initiated by placebo and nocebo interventions in

participants diagnosed with TTC, in comparison with age and sex matched healthy controls.

Saline solution was given intravenously (i.v.) three times in a row. The whole sample was consecutively told to first get an inert substance (neutral/control intervention), secondly a drug that would strengthen heart related functions (placebo intervention), and finally a drug that would be demanding for the heart (nocebo intervention).

Increasing effects on SBP could be detected as a reaction to both, the placebo and nocebo interventions in both groups, whereas DBP remained unaffected. Interestingly an anticipatory increase of HR could be seen before the nocebo intervention in both groups. Further the hypothesis that a specific sympathetic disposition in TTC patients could lead to an intensified response to the described interventions, could not be substantiated by means of our study design.

The aim of the second study was the investigation of physical and psychosocial long-term consequences in TTC patients compared to sex and age-matched patients after MI. Results were further contrasted to results of a norm sample.

Both patient groups were subjected to standardized questionnaires assessing quality of life, depression and anxiety, chronic stress, social support and resilience. Afterwards, collected parameters were compared between groups and with results of norm samples. This investigation showed that regardless of the different underlying pathophysiology, TTC is similarly associated with a severe, negative impairment in regard to mental and physical wellbeing as MIs.

4 Zusammenfassung

Die Stressinduzierte Kardiomyopathie, auch Tako-tsubo-Kardiomyopathie (TTC) genannt, ist eine seltene Form der primären Herzmuskelerkrankungen, von der hauptsächlich Frauen in der Postmenophase betroffen sind (Pilgrim & Wyss, 2008; Templin et al., 2015).

Trotz umfangreicher Bemühungen sind, 30 Jahre nach der ersten Beschreibung der TTC in Japan, Erkenntnisse über die zugrundeliegende Pathophysiologie begrenzt und die Ätiologie der TTC ist noch nicht vollständig verstanden (Sato, 1990). Es hat sich gezeigt, dass den Veränderungen des Herzmuskels oft ein physisches oder emotionales Stressereignis vorangegangen zu sein scheint (Templin et al., 2015).

Studienergebnisse zu affektiven Komorbiditäten bei TTC-Patienten sind, im Gegensatz zu psychosozialen Faktoren bei kardiovaskulären Erkrankungen, begrenzt (Ladwig et al., 2013; Pedersen et al., 2017; von Känel, 2016). Interessanterweise deuten erste Untersuchungen auf eine erhöhte Prävalenz psychischer Beeinträchtigungen, wie Depressions- oder Angstsymptome bei TTC-Patienten hin (Delmas et al., 2013; Elesber et al., 2007; Mudd et al., 2007; Summers et al., 2010).

Placebo und Noceboeffekte auf eine Vielzahl verschiedener Parameter, insbesondere im Zusammenhang mit Schmerz, sind umfassend untersucht und gut verstanden (Benedetti, 2014; Colloca et al., 2005). Psychosoziale Faktoren, die dem Kontext der therapeutischen Interaktion zugeordnet werden, sind in der Lage neurobiologische Veränderungen hervorzurufen, die den Veränderungen die bei der Einnahme pharmakologisch wirksamer Medikamente auftreten, sehr ähnlich sind (Kaptchuk & Miller, 2015; Meissner et al., 2011; Wager et al., 2004). Studien die Placebo- und Noceboeffekte auf herzbezogene Parameter untersuchen zeigen jedoch ambivalente Ergebnisse (Meissner, 2011).

Die vorliegende Dissertation besteht aus zwei Studien. Die erste Studie untersucht Placebo und Nocebo Effekte auf die subjektive Belastung (SUD), objektive herzbezogene Parameter (Herzrate, systolischer und diastolischer Blutdruck) und humorale Stressmarker (Copeptin und Cortisol) bei TTC-Patienten (n=20) im Vergleich zu herzgesunden Kontrollen (n=20). Es wurden drei aufeinanderfol-

gende Interventionen durchgeführt, bei denen Kochsalzlösung intravenös verabreicht wurde, begleitet von drei verschiedenen Suggestionen. Bei der ersten Intervention wurde den Probanden suggeriert, dass es sich bei der verabreichten Substanz um Kochsalzlösung handelte. Bei der zweiten Intervention, der Placebo-Intervention, wurde suggeriert, das Herz würde entlastet, es würde nun langsamer schlagen und der Blutdruck würde sinken. Zuletzt wurde die Nocebo-Intervention durchgeführt, mit der Suggestion, dass aufgrund der verabreichten Substanz eine Erhöhung der Herzfrequenz und des Blutdrucks erwartet würde.

Effekte der Placebo- und Nocebo-Interventionen wurde in beiden Gruppen gezeigt. Bei allen Teilnehmern nahm die subjektive Belastung nach der Nocebo-Intervention signifikant zu. Darüber hinaus wurde in beiden Gruppen ein Anstieg der Herzfrequenz vor der Nocebo-Intervention beobachtet. Dies ist vermutlich auf eine Erwartungsangst hinsichtlich der bevorstehenden negativen Intervention zurückzuführen, da die Reihenfolge der Interventionen bereits zum Zeitpunkt der Aufklärung bekannt gegeben wurde. Darüber hinaus stieg, als Reaktion auf beide, die positive und negative Intervention, der systolische Blutdruck in beiden Gruppen signifikant an. Die Erwartung der negativen Intervention, als letzter Teil der Untersuchung könnte erklären, warum durch die positive verbale Suggestion keine Entspannungseffekte auftraten. Signifikante Veränderungen des diastolischen Blutdrucks, von Cortisol und Copeptin traten nicht auf. Die beobachteten signifikanten Effekte der Interventionen auf den systolischen Blutdruck und die Herzrate, sowie die fehlenden Effekte auf den diastolischen Blutdruck stimmen mit den oben beschriebenen Studien überein.

Entgegen unserer Erwartung, unterschied sich die Reaktion auf die Interventionen nicht zwischen TTC-Patienten und herzgesunden Kontrollen. Die Hypothese, dass TTC-Patienten sensibler auf die Interventionen reagieren würden als die herzgesunde Kontrollgruppe und damit eine überdauernde, sympathische Disposition der TTC-Patienten, konnte durch das beschriebene Studiendesign nicht bestätigt werden. Dies könnte damit zusammenhängen, dass die Interventionen entweder ungeeignet oder nicht stark genug gewesen sind. Darüber hinaus könnte die medikamentöse Behandlung (z.B. mit Betablockern) einen dämpfenden Effekt auf die Aktivierung des sympathischen Nervensystems gehabt haben und damit mögliche Unterschiede zwischen den Patientenkollektiven gehemmt haben.

In der zweiten Studie wurden TTC-Patienten (n=68) und MI-Patienten (n=68) untersucht und die Ergebnisse mit den Daten einer Normstichprobe verglichen. Ein umfangreicher Katalog standardisierter Fragebögen wurde verwendet, um die Lebensqualität (Kansas City Cardiomyopathy Questionnaire (KCCQ), Kurzform-12, (SF-12)), Depressions- und Angstsymptome (Patients Health Questionnaire (PHQ-4)), chronischen Stress (Trier Inventory for Chronic Stress (TICS)), soziale Unterstützung (ENRICHD Social Support Instrument (ESSI)) und Resilienz (Resilience Scale (RS-5)) zu erfassen.

Bei keinem dieser Parameter unterschieden sich die beiden Patientengruppen signifikant voneinander. Beide Patientengruppen wiesen jedoch im Vergleich zur Normstichprobe eine signifikant schlechtere physische und psychische Lebensqualität (SF-12, KCCQ), höhere Werte auf den Depressions- und Angstskalen (PHQ-4) und erhöhten chronischen Stress (TICS) auf. Die Patientengruppen unterschieden sich in Bezug auf die soziale Unterstützung nicht von der Normstichprobe, jedoch zeigten sich höhere Resilienzwerte in der untersuchten Stichprobe. Letzteres könnte durch ein so genanntes posttraumatisches Wachstum erklärt werden. Es konnte zudem gezeigt werden, dass das Ausmaß der belastenden Ereignisse vor dem Ausbruch der Erkrankung in beiden Patientengruppen signifikant mit dem wahrgenommenen chronischen Stress und der psychischen Lebensqualität zum Zeitpunkt der Datenerhebung (im Durchschnitt etwa 5 Jahre nach der Akutphase) assoziiert war. Dies legt nahe, dass die Anzahl der belastenden Ereignisse nicht nur einen Risikofaktor für die Entwicklung der Herzerkrankungen darstellt, sondern sich auch negativ auf die langfristige Lebensqualität auswirkt.

In jedem Fall weisen die Ergebnisse auf die Notwendigkeit einer langfristigen körperlichen als auch psychologischen Versorgung für beide Patientengruppen hin, um die Patienten bei der Bewältigung von chronischem und akutem Stress zu unterstützen.

5 Summary

Stress-induced cardiomyopathy, also called Tako-tsubo cardiomyopathy (TTC), is an infrequent form of primary heart muscle diseases, mainly affecting postmenopausal women (Pilgrim & Wyss, 2008; Templin et al., 2015). Despite extensive efforts, 30 years after the first description of TTC in Japan, knowledge of underlying mechanisms is still limited and the etiology of TTC is not yet completely understood (Sato, 1990). It has been observed that the alterations of the heart muscle, that characterize the disease, are often preceded by a physical or emotional stress event (Templin et al., 2015).

Knowledge on psychosocial comorbidities in TTC patients is still limited, in contrast to psychosocial factors in the field of CVD (Ladwig et al., 2013; Pedersen et al., 2017; von Känel, 2016). Interestingly first studies indicate an increased likelihood for mental impairments, such as depressive or anxiety symptoms in TTC patients (Delmas et al., 2013; Elesber et al., 2007; Mudd et al., 2007; Summers et al., 2010).

Placebo and nocebo effects on a variety of conditions, especially related to pain have been extensively studied and are well understood (Benedetti, 2014; Colloca et al., 2005). Psychosocial factors that can be allocated to the context of the therapeutic interaction, are able to induce neurobiological changes, that are very similar to changes that occur when taking pharmacologically active drugs (Kaptchuk & Miller, 2015; Meissner et al., 2011; Wager et al., 2004). However, studies that investigated placebo and nocebo effects on heart related parameter show ambivalent results (Meissner, 2014).

The present dissertation consists of two studies. The first study investigated placebo and nocebo effects on subjective units of distress (SUD), objective cardiac parameters (HR, SBP, DBP), and humoral stress markers (copeptin and cortisol) in TTC patients (n=20) compared to heart-healthy controls (n=20). Three consecutive interventions were performed in which saline solution was administered (i.v.), accompanied by three different suggestions. During the first intervention, subjects were informed that the administered substance was saline solution and that this was used as a control intervention. Within the second intervention, the placebo intervention, it was suggested that the heart would be relieved, it could beat more slowly and BP would decrease. Finally, the nocebo intervention was

carried out, suggesting that an increase of HR and BP would be expected, due to the administered substance.

Effects of the placebo and nocebo interventions could be demonstrated in both groups. In all participants subjective distress increased significantly after the nocebo intervention. In addition, an increase in HR was observed before the nocebo intervention in both groups. This was presumably due to an anticipatory anxiety regarding the upcoming "stressful" intervention, since the order of the interventions was already revealed at the time of the clarification. Additionally, as a reaction to both, the positive and negative intervention SBP raised significantly in both groups. Expecting the negative intervention, as the final part of the investigation, could be an explanation that no relaxation effects occurred after the positive verbal suggestion. DBP, cortisol and copeptin did not change significantly. The observed significant effects of the interventions on SBP and HR, as well as the lacking effects on DBP are consistent with previous studies described above.

In contrast to our expectations, responses to the interventions did not differ between TTC patients and heart-healthy controls. The hypothesis that TTC patients would react more sensitively to the interventions than the heart-healthy control group and consequently a lasting sympathetic disposition of TTC patients could not be confirmed by the described study design. This could be related to the interventions being either inappropriate or not sufficiently strong. In addition, medication use (e.g. beta-blocker) may have had a diminishing effect on the activation of the sympathetic nervous system and thus might have inhibited differences between patient collectives.

The second study examined TTC patients (n=68) and MI patients (n=68), matched for age and sex, and compared the results with data of a norm sample. An extensive catalog of standardized questionnaires was used to assess quality of life (Kansas City Cardiomyopathy Questionnaire (KCCQ), Short Form-12, (SF-12)), depression and anxiety symptoms (Patients Health Questionnaire (PHQ-4), chronic stress (Trier Inventory for Chronic Stress (TICS)), social support (ENRICHD Social Support Instrument (ESSI)), and resilience (Resilience Scale (RS-5)).

In none of these parameters the two patient groups differed significantly from each other. However, both groups of patients showed a significantly worse physical and mental quality of life (SF-12, KCCQ), higher rates of depression and anxiety symptoms (PHQ-4) and increased chronic stress (TICS) compared to the norm sample. The patient groups did not differ from the norm sample in terms of social support, but higher resilience rates were shown. The latter could be explained by a so-called post-traumatic growth.

It could be shown that the amount of stressful events before the onset of the disease was significantly associated with the perceived chronic stress and the mental quality of life at the time of data collection (on average about 5 years after the acute phase) in both patient groups. This proposes that the number of stressful events is not only a risk factor for the development of the heart disease, but has an impact on the long-term quality of life. In any case, the results indicate long-term physical and psychological care, for both groups of patients to support them in coping with chronic and acute stress.

6 Paper I

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 02 August 2019
doi: 10.3389/fpsyt.2019.00549

Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls

Elisabeth Olliges[1†], Simon Schneider[2†], Georg Schmidt[2], Daniel Sinnecker[2,3], Alexander Müller[2], Christof Burgdorf[4,5], Siegmund Braun[6], Stefan Holdenrieder[6], Hansjörg Ebell[7], Karl-Heinz Ladwig[8,9], Karin Meissner[1,10‡], and Joram Ronel[8,11‡]*

[1] Institute of Medical Psychology, Medical Faculty, LMU Munich, Munich, Germany, [2] Medizinische Klinik und Poliklinik I, Klinikum rechts der Isar, Technische Universitaet Munich, Munich, Germany, [3] German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, Munich, Germany, [4] Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum Munich, Technische Universitaet Munich, Munich, Germany, [5] Department of Cardiology, Heart and Vascular Centre Bad Bevensen, Bad Bevensen, Germany, [6] Institute of Laboratory Medicine, Deutsches Herzzentrum Munich, Technische Universitaet Munich, Munich, Germany, [7] Private Practitioner, Munich, Germany, [8] Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universitaet Munich, Munich, Germany, [9] Department of Epidemiology II, Helmholtz Zentrum, Munich, Germany, [10] Division of Health Promotion, Coburg University of Applied Sciences, Coburg, Germany, [11] Department of Psychosomatic Medicine, Klinik Barmelweid AG, Barmelweid, Switzerland

OPEN ACCESS

Edited by:
Seetal Dodd,
Barwon Health, Australia

Reviewed by:
Karl Bechter,
University of Ulm, Germany
Victor Chavarria,
Parc Sanitari Sant Joan de Déu, Spain

***Correspondence:**
Elisabeth Olliges
Elisabeth.Olliges@med.uni-muenchen.de
Joram Ronel
j.ronel@tum.de

†These authors have contributed equally to this work and share first authorship.

‡These authors have contributed equally to this work and share senior authorship.

Specialty Section:
This article was submitted to Psychosomatic Medicine, a section of the journal Frontiers in Psychiatry

Received: 14 December 2018
Accepted: 15 July 2019
Published: 02 August 2019

Citation:
Olliges E, Schneider S, Schmidt G, Sinnecker D, Müller A, Burgdorf C, Braun S, Holdenrieder S, Ebell H, Ladwig K-H, Meissner K and Ronel J (2019) Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. Front. Psychiatry 10:549. doi: 10.3389/fpsyt.2019.00549

The etiology of takotsubo cardiomyopathy (TTC)—a rare, reversible, and acquired form of cardiac diseases—is not yet fully explained. An exaggerated activation of the sympathetic-nervous-system (SNS) following stressful psychosocial life events is discussed to be of key importance. In this experimental study, we tested whether TTC patients, compared to heart-healthy controls, respond more strongly to supporting placebo interventions and stressful nocebo interventions targeting cardiac function. In a single experimental session, 20 female TTC patients and 20 age matched (mean age 61.5 years, ± 12.89) catheter-confirmed heart-healthy women were examined. Saline solution was administered three times i.v. to all participants, with the verbal suggestion they receive an inert substance with no effects on the heart (neutral condition), a drug that would support cardiac functions (positive condition), and a drug that would burden the heart (negative condition). Systolic and diastolic blood pressure (DBP/SBP), heart rate (HR), endocrine markers cortisol (µg/dl), copeptin (pmol/l), and subjective stress ratings (SUD) were assessed to examine alterations of the SNS and the hypothalamic–pituitary–adrenal axis (HPA). Before and after each intervention SUD was rated. One pre and three post serum cortisol and copeptin samples were assessed, and a long-term electrocardiogram as well as non-invasive, continuous blood pressure was recorded. The study design elucidated a significant increase of SUD levels as a response to the nocebo intervention, while perceived stress remained unaffected during the preceding neutral and positive interventions. Increasing SUD levels were accompanied by higher SBP and an anticipatory increase of HR shortly prior to the nocebo intervention. SBP increased also as a response to positive verbal suggestions (Bonferroni-corrected p-values > .05). Alterations of cortisol and copeptin due to the interventions and significant placebo effects failed to appear. Interestingly no

differences between TCC patients and controls could be found.These findings do not support the assumption of an exaggerated activation of the SNS as a discriminatory factor for TTC. Since especially the nocebo intervention revealed negative subjective and objective effects, our results underscore the urgent need to consider carefully the impact of verbal suggestions in the interaction with cardiac patients in daily clinical routine. This study is registered at the Deutsches Register Klinischer Studien (DRKS00009296).

Keywords: placebo effects, nocebo effects, takotsubo cardiomyopathy, cardiological response, sympathetic nervous system

INTRODUCTION

Placebo effects are conceptualized as neurobiological phenomena, resulting from the positive psychosocial context, a treatment is embedded in. Correspondingly, a negative psychosocial context may induce negative clinical outcomes, referred to as "nocebo effects." The current state of research suggests that placebo and nocebo effects are mediated by explicit expectations and shaped by different means; social observational learning (1), classical conditioning (2), and verbal suggestions (3). The doctor's verbal suggestions inducing positive or negative outcome expectations are an important feature for placebo and nocebo effects (4–7). Placebo effects on functions linked to the central nervous system (CNS) such as pain or Parkinson's disease have been extensively investigated and their mechanisms are well understood (6, 8). For example, placebo analgesia is often associated with the release of endogenous opioids, whereas placebo-induced motor improvement in patients with Parkinson's disease could be connected to the release of dopamine in the dorsal striatum (8, 9). Within several studies, it has been demonstrated that placebo interventions can also affect peripheral organ functions (e.g., pulmonary and cardiovascular functions) controlled by the autonomic nervous system (ANS) (10–13), but results in this neglected area of placebo research are often ambiguous. For example, significant effects of verbal suggestions specifically targeting the diameter of coronary arteries could be observed during a coronary angiography. Here participants received intracoronary saline injections, together with the verbal suggestion the "drug" would widen the heart vessels and improve cardiac perfusion. Interestingly, the verbal suggestion led to coronary vasoconstriction accompanied by chest pain reduction. Acute psychological burden, HR and BP did not change significantly. Authors concluded that the coronary vasoconstriction was not caused by increased stress levels but by a reduction of sympathetic outflow and/or increase of parasympathetic outflow to the cardiac vessels (12).

Takotsubo cardiomyopathy (TTC) (also referred to as "stress-induced cardiomyopathy" or "broken heart syndrome") is considered a very rare, reversible, and acquired form of primary myocardial disorders (14–16). TTC is characterized by an acute, functional disturbance in the contraction of the myocardium, primarily affecting mid and apical areas of the left ventricle, accompanied by symptoms and signs rather similar to those of the acute phase of a myocardial infarction (MI) (e.g., chest pain, dyspnea or alterations in the electrocardiogram or cardiac markers such as troponin), while the coronary arteries are mostly unaffected in TTC patients (17). Medeiros and colleagues found a similar impairment of systolic and diastolic function in TTCs and post MI patients, despite of their completely different pathophysiology (18). An increased sympathetic tone as well as a concomitant enhanced myocyte and microvascular catecholamine sensitivity is considered to increase the individual's vulnerability and may therefore serve as a risk factor for the development of TTC (19).

Approximately 0.07–2.3% of patients, suspected with an acute coronary syndrome (ACS), are diagnosed with TTC after cardiac catheter examination, with almost 90% being postmenopausal women (14, 20–24). The etiology of TTC is not yet fully explained. A dysfunctional presentation and processing of external physiological or psychosocial stressors are assumed to initiate an inadequate activation of the sympathetic nervous system, and therefore a pathophysiological cascade of the TTC-patient's myocardium (23, 25, 26). Triggers are not necessarily negative. A very small percentage of TTC patients (approximately 4%) experience a positive life event (e.g. a birthday party or the child's wedding), prior to the onset of the disease. It is supposed that, positive as well as negative events are proceeding through analogous signal pathways in the central nervous system (26, 27).

Further, data on the recurrence of TTC varies, but relapses are not infrequent with approximately 1.5% to 2.4% per patient-year and a rate of 5% to 11.4% within the first 4 years (25, 28–30). Simultaneously, several studies found a significantly higher mortality rate in TTCs in comparison with a control group of the same age and sex (25, 31, 32). Apart from cardiovascular events, this appears to be due to an increased prevalence of non-cardiac comorbidities, which suggests a persistent pathology, presumably referring to an alteration of the sympathetic system, inherent in TTC patients (28, 33–36).

Based on these considerations, we investigated whether the cardiac regulation of TTC patients reacts more sensitively to positive and negative external stimuli than that of heart-healthy individuals. In a case–control study, we examined the cardiovascular response to placebo and nocebo interventions targeting the cardiac functions in 20 TTC patients on average two years after disease onset and 20 matched heart-healthy individuals. We hypothesized that in TTC patients cardiovascular and perceived stress parameters would be stronger regulated as a response to placebo and nocebo interventions compared to healthy individuals.

MATERIAL AND METHODS

Sample

This case–control study (controlled for age) included 20 women, diagnosed with TTC, and 20 volunteers (CG) free of significant coronary artery disease (vessel stenosis ≤30%, confirmed via heart catheterization in the past) (see **Table 1**). TTC patients were diagnosed regarding Mayo Clinic's diagnostic criteria for Takotsubo Cardiomyopathy. These are: 1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities extending beyond a single epicardial vascular distribution, with a stressful trigger often, but not always present, 2) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture, 3) new electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin, 4) absence of a pheochromocytoma or myocarditis (37). Participants with significantly decreased ejection fraction (<55%) or low German proficiency, were excluded from the study. The mean time interval between the episode of TTC and the participation in the study was 24.61 months (±22.8). A total of 40 eligible women diagnosed at "Deutsches Herzzentrum" and "Medizinische Klinik und Poliklinik I, Klinikum rechts der Isar," Technical University, Munich, were enrolled in the study and contacted *via* mail and followed-up by a phone call. The study protocol was approved by the institutional review board. All participants received 50 € compensation, borne by the Deutsches Herzzentrum, Munich.

TABLE 1 | Baseline characteristics.

Characteristic	TTC	Controls	*p*
Age (years), *Mean (SD)*	61.65 (14.1)	61.35 (11.67)	.94†
Time point of examination *(n)*			.43††
09:00 am	5	8	
11:00 am	11	7	
01:00 pm	4	5	
Living in a relationship *(n)*	18	16	.64††
Number of children, *Median (IQR)*	2 (1–2)	1.5 (1–2)	.94†
Living condition *(n)*			
Alone	5	7	.73††
With partner and/or children	13	11	.51††
With children	4	7	.48††
Employment situation *(n)*			.64††
Fulltime	6	5	
Part time > 50%	2	5	
Part time < 50%	0	1	
Unemployed	1	0	
Retired	8	7	
Full time household	2	2	
Short Form Health Survey (SF-12)			
Physical component summary score (PCS)	55.8 (19.8)	50.3 (19.2)	.43†
Mental health component summary score (MCS)	56.2 (20.2)	51.3 (19.3)	.45†
Time since diagnosis (months), *Mean (SD)*	24.61 (22.8)		

Values are mean ± SD or n (%). †Mann–Whitney–U test, ††Chi-square-Test.

Endpoints

The following parameter were chosen as primary endpoints in order to indicate alterations of the SNS and the HPA, the main peripheral pathways of the human stress system: Non-invasive continuous systolic (SBP) and diastolic blood pressure (DBP) as well as heart rate (HR) measured with Finapress Nova device (Finapres Medical Systems B.V.), as established indicators for the adaptive response to altered environmental, bio-psycho-social stimuli. Both cardiac functions are self-modifiable to attune the delivery of oxygenated blood by augmenting the beating frequency, respectively the pressure, with which the blood is pumped through the arteries (38). In addition, perceived stress was assessed by the "subjective units of distress scale" (SUD), an 11-point numeric rating scale from 0 (no stress) to 10 (maximal stress). Furthermore, blood samples were taken to measure cortisol (µg/dl) and copeptin (pmol/l). Cortisol has been shown to be proportionate to the degree of stress on a peripheral level. To gain a more direct insight in the stress level on the cerebral level, copeptin was chosen as a second humoral stress marker. Copeptin, a pre-hormone of vasopressin, is considered a relevant marker for acute, endogenous stress, especially associated with cardiological diseases (e.g. myocardial infarctions) (39–42).

Procedure

The experiment was performed in the Department of Cardiology at Klinikum rechts der Isar, between 10:00 am and 1:00 pm in a cardiological outpatient lab. Participants were examined at different time points with no contact to each other; therefore an exchange of experiences during the experiment was not possible and no "placebo-by-proxy" effects could emerge (43). After obtaining informed consent, participants received a transthoracic echocardiography to assess standard parameters [e.g., septum thickness (mm) and ejection fraction (%)]. Thereafter, the study coordinator connected the participants to the Finapress Nova device (Finapres Medical Systems B.V.) and activated the continuous measurement of cardiovascular parameters [blood pressure (mmHg), heart rate (bpm)] while the attending physician established vascular access and took the first blood sample [cortisol (µg/dl) and copeptin (pmol/l)] (see **Figure 1**).

At the beginning of the experiment (M_0), the participants were asked to rate their perceived stress (SUD). After a baseline measurement of approximately 5 min, during which the cardiological parameters were continuously assessed, the first sham-intervention took place (I_1). Here, the physician administered 2 ml of 0.9% physiological saline solution (NaCl) intravenously together with a standardized verbal neutral suggestion that the intravenously administered solution would not cause any bodily changes "similar to taking a sip of water." Thereafter, the first post-intervention measurement of physiological parameters was performed (approximately 5 min). At the end, patients were asked again to rate their level of distress on an 11-point numeric rating scale (from 0 = no stress to 10 = maximal stress) and blood samples were taken for a second time (M_2). Subsequently, the same procedure was performed for the placebo and the nocebo interventions: after a pre-intervention measurement of physiological parameters of approximately 5 min

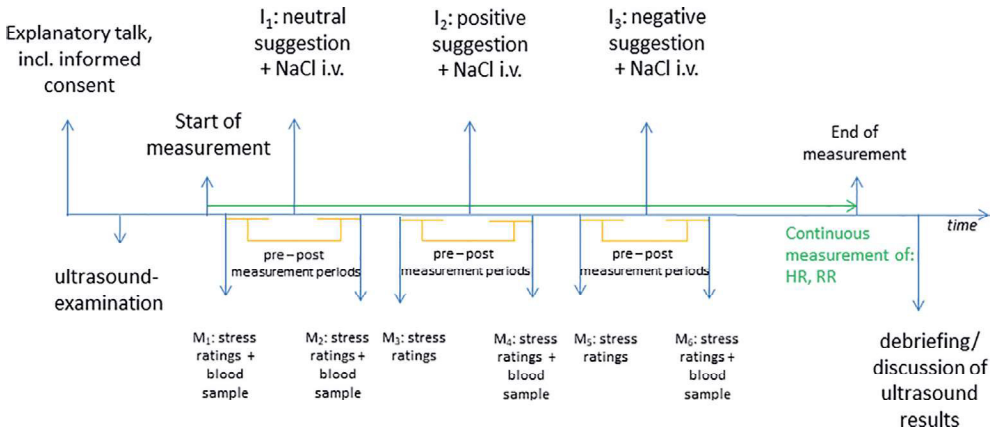


FIGURE 1 | Procedure. M, Measurement; I, Intervention; HR, heart rate; RR, blood pressure.

patients were asked to rate perceived stress levels (SUD) (M_3). Next, 2 ml NaCl was administered intravenously accompanied by a standardized verbal positive suggestion that the intervention would "strengthen the heart," "blood pressure and heart rate would decrease," and "breathing would become easier" as the body would be "better supplied with oxygen" (I_3). Then another post-intervention measuring period (approximately 5 min) was obtained with continuous measurement of physiological parameters. At the end of this period, distress levels were assessed and blood samples were taken (M_4). Again after a pre-intervention period of approximately 5 min, stress ratings (SUD) were assessed again (M_5). Finally, the last 2 ml NaCl was administered analogously to the previous conditions, with the verbal suggestion that this intervention would "burden" the heart, it would need to work "stronger and faster," and "hot flashes" could occur (I_5). Conclusively, the last post-intervention period (approximately 5 min) was performed with continuous measurement of physiological parameters and assessment of distress levels, and the last blood sample was taken (M_6). At the end of the examination the study rationale was disclosed to the participants and they were informed about the placebo character of the study with the administered substance being only "water." Additionally, the individual echocardiography results were reviewed together with the patient.

Statistical Analysis

Analyses were performed by means of IBM SPSS Statistics 25 with a p-value ≤ 0.05 considered as significant. Mean values of HR, SBP, and DBP were calculated for the period from 200 to 20 s prior to the interventions (pre values) and 20 to 200 s after the interventions (post values). Data that did not fit normal distribution were logarithmized. Pre-post changes of HR, SBP, and DBP induced by the neutral, positive, and negative interventions were compared between groups by means of a mixed-design ANOVA with the within-subject factors "time" (pre and post intervention) and "condition" (neutral, positive, and negative), and the between-subject factor "group" (TTC, controls). Subsequently Bonferroni-corrected *post hoc* tests were performed. Due to the absence of a normal distribution, SUD levels were evaluated by using Bonferroni-corrected Wilcoxon signed-rank tests and Kruskal–Wallis tests, respectively; changes of cortisol as well as copeptin levels were calculated using Wilcoxon signed-rank tests, Mann–Whitney–U, and Friedman tests.

RESULTS

Baseline Characteristics

TTC patients and controls were comparable with regard to age, employment situation, living situation, and quality of life. The time point of evaluation did not differ between groups and the mean time span between the TTC diagnosis and the examination was 24.61 months (±22.8) (**Table 1**).

Subjective Units of Distress (SUD)

SUD changes from before to after the neutral, positive, and negative intervention were evaluated by using the Wilcoxon signed-rank tests. No significant changes were observed in response to the neutral and positive verbal suggestions (Bonferroni-corrected $p = .1$ and $p = .06$, respectively). However, SUD ratings increased in response to the negative verbal suggestion (Bonferroni-corrected $p < .001$), indicating a nocebo effect on perceived stress. SUD did not differ between patients with a history of TTC and heart-healthy controls at any time point during the experiment (Mann–Whitney–U test, all Bonferroni-corrected $p > .05$) (**Figure 2** and **Table 2**).

Systolic Blood Pressure (SBP)

The mixed-design ANOVA with the within-subject factors "time" (pre, post intervention) and "condition" (neutral, positive, negative) and the between-subject factor "group" (TTC, controls) was used to examine SBP levels. A significant interaction between

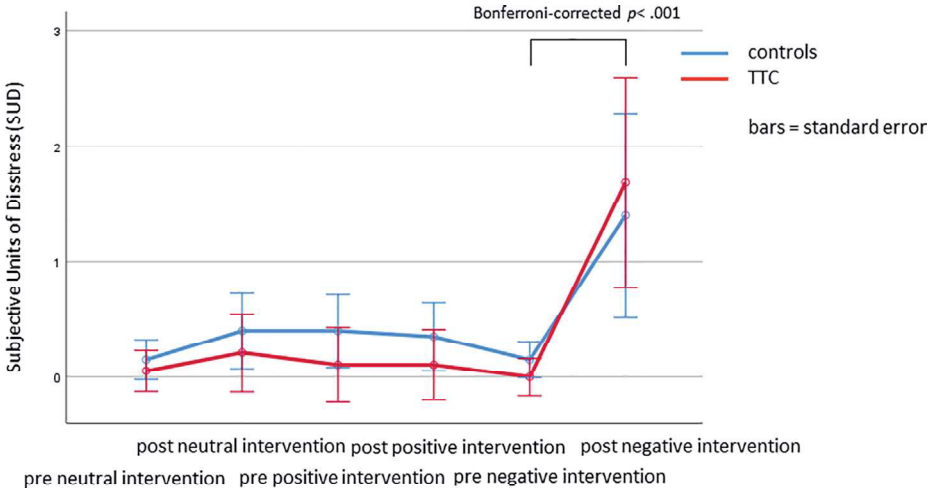


FIGURE 2 | Subjective Units of Distress (means ± SD) before and after the neutral, positive, and negative interventions.

TABLE 2 | Subjective Units of Distress (SUD), systolic blood pressure (mmHg).

Time point	TTC		Controls	
Subjective Units of Distress (SUD)	**Mean**	**SD**	**Mean**	**SD**
Pre neutral suggestion	.15	.49	.05	.22
Post neutral suggestion	.4	.88	.2	.52
Pre positive suggestion	.4	.88	.1	.45
Post positive suggestion	.35	.81	.1	.45
Pre negative suggestion	.15	.49	.0	.0
Post negative suggestion	1.4	1.1	1.6	1.1
Systolic blood pressure (mmHg)				
Pre neutral suggestion	120.37	10.86	127.01	18.42
Post neutral suggestion	118.62	8.61	123.11	19.01
Pre positive suggestion	120.45	17.1	130.63	26.47
Post positive suggestion	124.87	13.8	131.53	56.53
Pre negative suggestion	127.72	13.93	125.13	20.42
Post negative suggestion	134.82	22.36	129.1	21.03
Pre neutral suggestion	120.37	10.86	127.01	18.42
Diastolic blood pressure (mmHg)				
Pre neutral suggestion	57.17	13.71	61.6	11
Post neutral suggestion	58.0	11.83	59.16	11.1
Pre positive suggestion	53.68	8.6	60.04	13.45
Post positive suggestion	55.62	7.29	59.67	13.41
Pre negative suggestion	57.91	10.41	59.56	13.21
Post negative suggestion	59.1	10.69	61.39	13.23
Heart rate (bpm)				
Pre neutral suggestion	54.38	5.46	55.34	7.44
Post neutral suggestion	55.74	5.61	56.95	7.76
Pre positive suggestion	57.92	9.05	56.17	8.32
Post positive suggestion	58.69	8.47	57.57	8.63
Pre negative suggestion	58.21	9.29	57.69	8.73
Post negative suggestion	58.53	8.86	57.63	8.48
Cortisol (µg/dl)				
Pre neutral suggestion	13.23	5.46	14.05	7.44
Post neutral suggestion	12.87	5.61	13.54	7.76
Post positive suggestion	12.37	8.47	13.08	8.63
Post negative suggestion	11.99	8.86	12.81	8.48
Copeptin (pmol/l)				
Pre neutral suggestion	54.38	20.82	55.34	20.73
Post neutral suggestion	55.74	20.83	56.95	20.65
Post positive suggestion	58.69	20.92	57.57	20.66
Post negative suggestion	58.53	20.80	57.63	20.75

"time" and "condition" was found ($F_{(2,76)}$ = 14.09; p < .001). *Post hoc* tests showed higher SBP levels in response to the negative and the positive verbal suggestions as compared to the neutral verbal suggestion (Bonferroni-corrected p-values, p = .045 and p = .002, respectively). There was also a significant main effect for "condition" ($F_{(2,76)}$ = 3.2, p = .047). Bonferroni-corrected *post hoc* tests, however, revealed no significant difference between conditions. No other main or interaction effects were significant (**Figure 3** and **Table 2**).

Diastolic Blood Pressure (DBP)

The mixed-design ANOVA for DBP levels with the within-subject factors "time" (pre andf post intervention) and "condition" (neutral, positive, and negative) and the between-subject factor "group" (TTC and controls) revealed no significant main or interaction effects (**Figure 4** and **Table 2**).

Heart Rate (HR)

The mixed-design ANOVA with the within-subject factors "time" (pre and post intervention) and "condition" (neutral, positive, and negative) and the between-subject factor "group" (TTC and controls) for HR levels revealed a significant interaction effect between "time" and "condition" ($F_{(2,76)}$ = 5.5; p = .01). Simple effects analyses showed that this interaction was due to higher HR levels before the negative verbal suggestion compared to before the positive verbal suggestion, indicating an anticipatory increase of HR (Bonferroni-corrected p = .02). Furthermore, a significant main effect of "condition" was found ($F_{(2,78)}$ = 5.11, p = .01), with higher HR levels in the nocebo condition compared to the neutral condition (Bonferroni-corrected p = .037). Finally, the main effect of "time" was significant ($F_{(1,39)}$ = 46.8, p < .001), which was due to increasing HR levels from before to after the intervention (estimated means ± SE, before: 56.5 ± 1.2 and after: 57.4 ± 1.2). No other main or interaction effects were significant (**Figures 5**, **6** and **Table 2**).

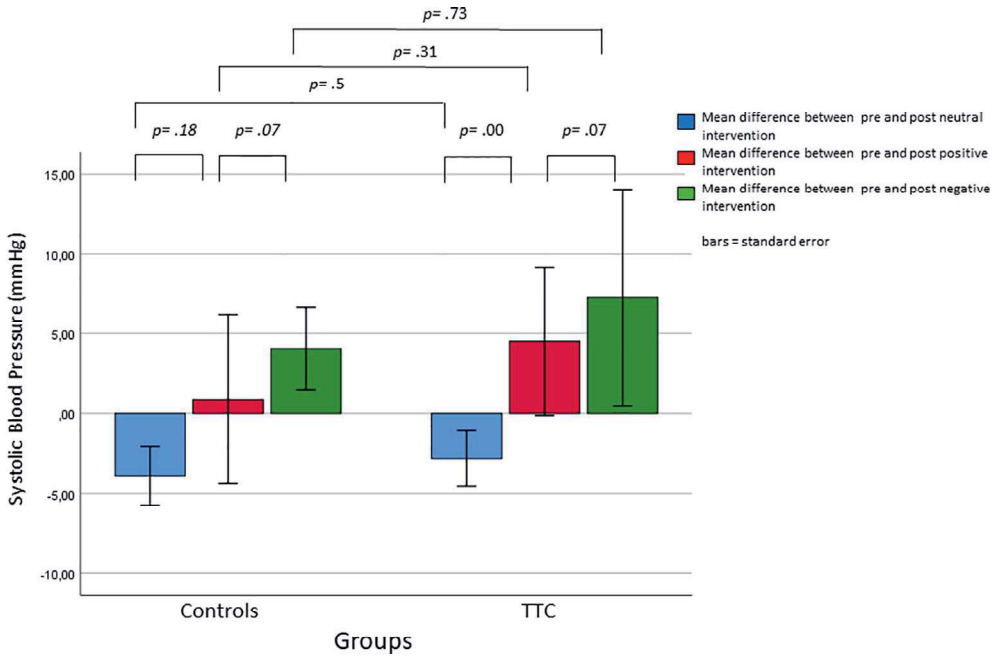


FIGURE 3 | Changes in systolic blood pressure in response to the neutral, positive, and negative placebo interventions.

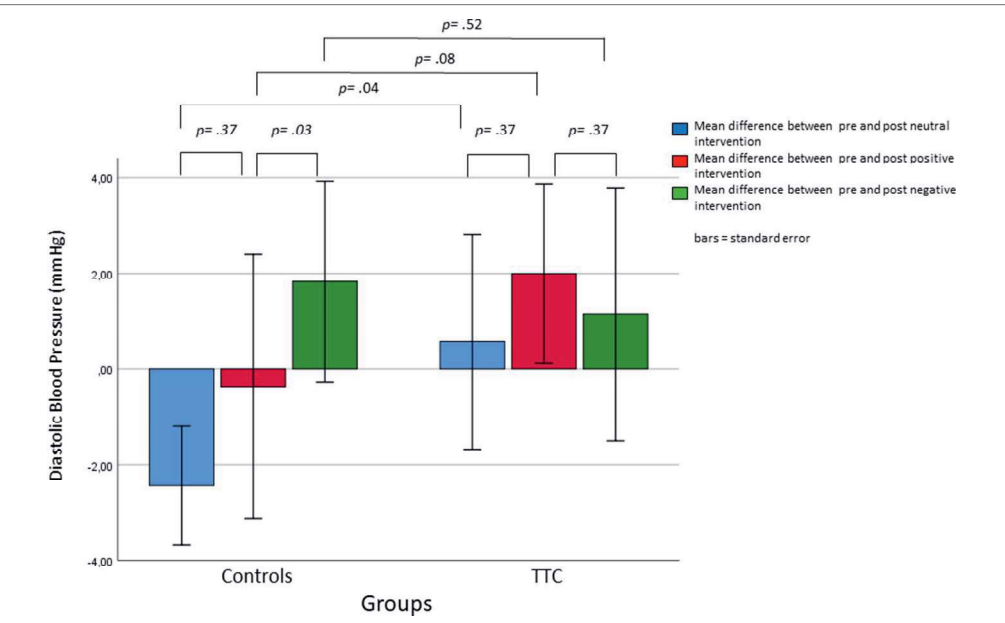


FIGURE 4 | Changes diastolic blood pressure in response to the neutral, positive, and negative placebo interventions.

Humoral Stress Markers

Cortisol levels at baseline and after the neutral, the positive and the negative verbal suggestions were compared by Friedman tests. Results revealed a significant difference between conditions ($x^2 = 64.3$, $p < .001$), which was due to a significant decrease of cortisol levels from condition to condition (Wilcoxon tests, all Bonferroni-corrected $p < .001$). In no condition significant group differences between TTC patients and controls were observed (Mann–Whitney–U test, all Bonferroni-corrected p-values = 1) (**Table 2**). A Friedman test for copeptin levels at baseline and after the neutral, the positive and the negative verbal suggestions revealed no significant differences between conditions ($p = .84$). In no condition significant differences between TTC patients and controls were observed (Mann–Whitney–U test, all Bonferroni-corrected $p = 1$) (**Figure 7** and **Table 2**).

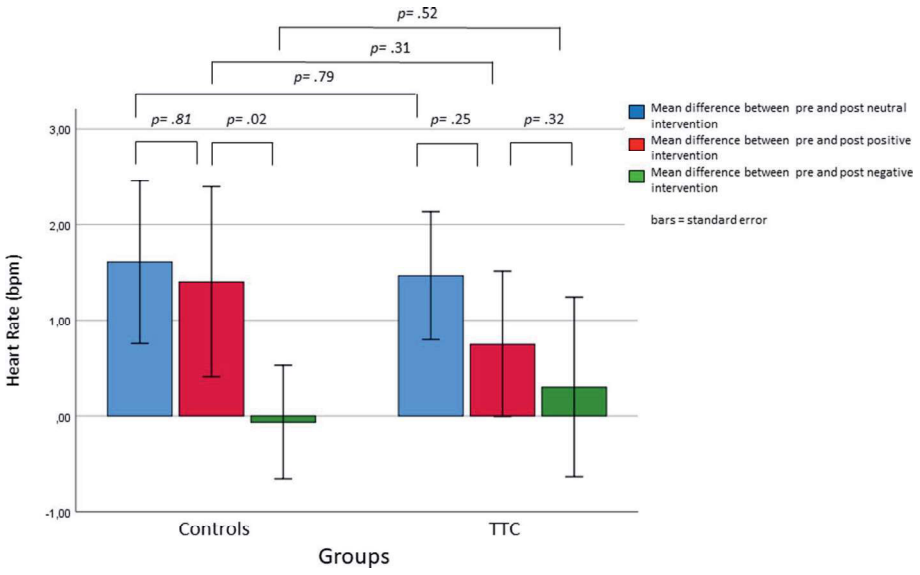


FIGURE 5 | Changes in heart rate in response to the neutral, positive, and negative placebo interventions.

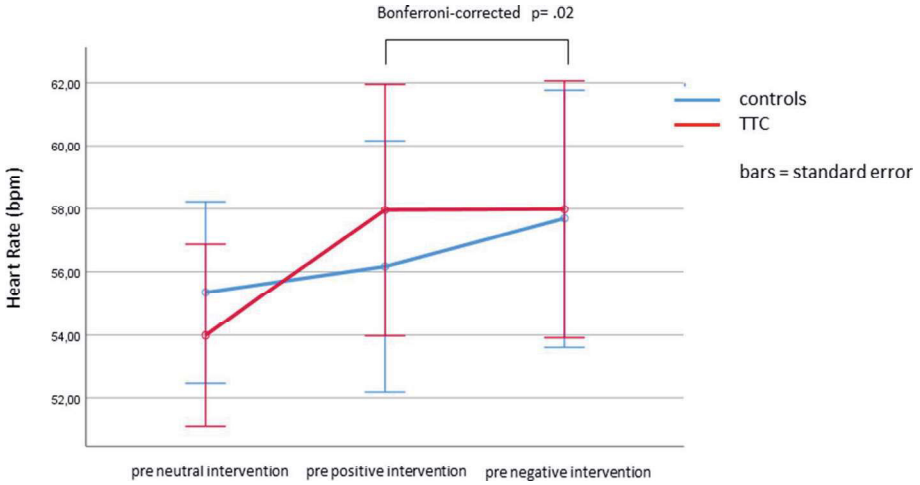


FIGURE 6 | Heart rate (bpm) during the anticipation phases (pre values) of the three interventions.

DISCUSSION

In this study, we investigated cardiac, psychological, and endocrine stress responses to placebo and nocebo interventions targeting the heart in patients with a history of TTC and matched heart-healthy controls. Although the pathophysiology underlying TTC is not yet entirely clear, a dysfunctional, overmodulated stress response with enhanced sympathetic stimulation might be of key importance (19). We expected that physiological and behavioral responses to placebo and nocebo interventions would be more pronounced in patients with a history of TTC compared to controls than in heart-healthy controls. In our study a significant nocebo effect on subjective units of distress was detected for the whole group of 40 participants. Furthermore, HR increased significantly before the nocebo intervention, possibly indicating anticipatory anxiety towards the upcoming negative intervention. In addition, SBP levels increased significantly in response to both, the placebo and nocebo interventions, suggesting a possible nocebo effect on SBP. Significant alterations of DBP, cortisol and copeptin due to the interventions failed to appear. Contrary to our expectations, none of these responses differed between TTC patients and heart-healthy controls.

Evidence regarding placebo effects on end organ functions regulated by the ANS (e.g., cardiovascular or gastric functions) is less clear compared to the accumulating evidence for placebo effects on functions associated with the central nervous system [e.g., pain and itch, e.g. Refs. (44–46)]. The

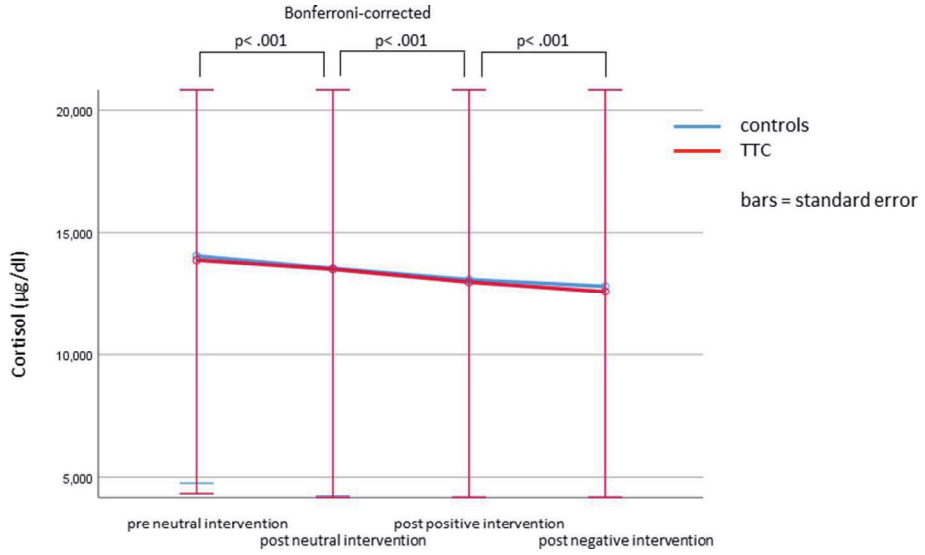


FIGURE 7 | Plasma cortisol levels according to interventions.

ANS is characterized by high functional specificity provided through elaborated afferent and efferent fibers. Hence, it is not surprising that placebo and nocebo interventions targeting end-organ functions controlled by the ANS can display a high target-specificity (10, 47). The present study adds to this field of placebo research in addressing cardiac parameters that are under control of the autonomic nervous system (HR, SPB, and DBP), as well as subjective stress ratings (SUD) and humoral correlates (copeptin and cortisol). To our knowledge this is one of the first experimental studies, and the first placebo study, in patients with a history of TTC.

Our observations of significant effects from placebo and nocebo interventions on SPB and HR but not on DBP are in accordance with previous studies, which investigated placebo and nocebo effects on cardiovascular parameters by means of verbal suggestions (13, 48). Former investigations that aimed to induce BP changes in healthy individuals by means of a placebo-spray in combination with verbal suggestions for instance, assumed that the absence of significant BP alterations could potentially be explained by lacking associations between memories of physiological or mental states with specific autonomic changes in the brain, which might be a necessary condition for verbal suggestions to induce the intended effects (49). This explanation was linked to the central organizational principle of the brain named, the "reuse of neural circuity," supposing that neural circuits established for a specific purpose, diversify or exploit to new uses, without losing their genuine function (50). This explanatory approach might also give insightful hints for the results of our study. A link between memories of BD and HR decreases and specific autonomic changes in the brain that could be crucial for the targeted physiological changes might not have been available.

Also the disclosure of the fixed order of the interventions, with the negative intervention being at the end, might have prevented the positive verbal suggestions to evoke HR and BP decrease. The increase of HR prior to the beginning of the nocebo intervention might be linked to the disclosure of the chronological order of interventions as well and could indicate anticipatory anxiety towards the nocebo intervention. Lyby and colleagues could show that fear can eliminate placebo effects induced by verbal suggestions (51). In this regard several imaging studies especially from the area of pain indicate that there is altered activity in the cortical nociceptor network already during the anticipation of pain (52, 53). Moreover, the perception of pain is not exclusively depending on the specific noxious stimulus. Attention, expectation and reappraisal seem to play an important role in the cognitive modulation of pain (54). Among other brain regions [e.g., dorsolateral prefrontal cortex (DLPFC) or the periaqueductal gray (PAG)], especially the rostral anterior cingulate cortex (rACC) seems to play an important role in the nociceptive network and reveals complex response patterns provoked by placebo interventions, but also during anticipation phases (55–59). An activation likelihood estimation meta-analysis also underlines the impact of negative expectations resulting from past experiences and present information on pain perception, which in turn might lead to higher pain intensity (60). Therefore, the anticipation of the negative intervention might explain the absence of relaxing effects due to the positive verbal suggestion and the increase of HR prior to the negative verbal suggestion. Nocebo effects (especially in the area of pain) have proven to be associated with complex biochemical and neuroendocrine mechanisms that seem to be connected to anticipatory anxiety (44). This suggests the activation of the HPA or SNS, which build the main peripheral pathways of the human stress system. The HPA axis regulates the release of cortisol that has been shown to be proportionate to the degree of stress on a peripheral level. In our study cortisol levels did not change as a response to the

interventions, as it could be seen in previous studies on nocebo hyperalgesia but "naturally" decreased during the examination (61, 62). A similar phenomenon could be seen in a study done by Meissner et al. who examined the predictive value of cortisol on motion sickness (63) or Benedetti et al. who showed that placebo and nocebo effects in cortisol secretion could not be induced by verbal suggestions, but were affected by pharmacological conditioning (3). A meta-analysis, again in the area of pain, showed that the combination of verbal suggestions and conditioning induces larger placebo and nocebo effects than verbal suggestions alone (64, 65). Colloca and colleagues concluded that conditioning is less important in nocebo hyperalgesia compared to placebo analgesia (1). Unintended expectations and stimulus pairings could have been developed through the TTC patient's experiences during their disease history that might have led to a "blending" of expectation- and conditioning-induced effects in our examination (66).

The question of whether TTC is a transient, reversible disease, or is based on an enduring pathology affecting the sympathetic nervous system, is not yet fully clarified. It is widely believed that the suspected, exaggerated sympathetic activation within the acute phase of TCC is triggered by a precedent, mostly unexpected stressful life event [e.g., Ref. (21)]. The assumption that the normalization of the shape of the left ventricle and the systolic LVEF is accompanied by a regulation of the underlying sympathetic activation, would in turn explain the lacking difference between TTCs and heart-healthy controls. Additionally, recent studies indicate that the exposure to repeated stressors (in contrast to a single life event) is associated with the onset of TTC (67, 68), the authors argued that long-term stressful conditions might have led to an increased vulnerability towards strong emotional or physical stressors triggering the development of TTC. Within our study, positive as well as negative interventions were announced far in advance, took place in the "save environment" of the hospital and might therefore not have served as suitable stimuli for an exaggerated activation of the sympathetic nervous system. Another recent study focused on altered β-adrenergic signaling in TTC cardiomyocytes derived from pluripotent stem cells to explore whether genetic susceptibility underlies the pathophysiology of TTC. These findings point at a complex, multifactorial etiology of TTC with genetic predispositions combined with environmental factors such as age, postmenopausal hormonal status and stressful life events (69). At the cellular level, Borchert and colleagues could demonstrate that TTC phenotype was associated with enhanced β-adrenergic signaling and higher sensitivity to catecholamine-induced toxicity (70). These considerations might be further promising regarding distinguishing features between TTC and heart healthy individuals.

Although the sample size of 20 TTC patients is comparably high considering the prevalence of 0.07–2.3% of patients suspected with an ACS, a larger number of participants in our study would have been desirable. As a further issue the participants' medication intake (e.g., β-blocker) needs to be considered. Although the intake of antihypertensive medication was relatively similar in both groups, this could have led to a dampening effect of sympathetic activation and might therefore have reduced differences between groups. Furthermore, in the light of the explanations above, a combining of classical conditioning and verbal suggestions might have improved especially the placebo response but also the nocebo response. It could have shed new light on the impact of conditioning and verbal suggestions (resp. explicit expectations) on placebo and nocebo effects within the autonomic nervous system. A further limitation might be the variety of time spans between the cardiac event and the investigation that is attributed to the low prevalence of TTC. If we would have included patients within their acute phase only, the recruitment period would have been enormously long, which would have meant that constancy in further parameters, for instance examiner or examination rooms, could not have been guaranteed. If TTC is seen as a reversible disease or a maintaining pathology in stress processing, a predefinition of one or more specific time points (e.g., within the acute phase together with a two-year follow-up) needs to be considered in a further study. Due to standardization resp. generalization reasons (especially considering the relatively small sample size) the chronological order of the three interventions was standardized. Future studies should consider a cross-over design with a randomized order. The observation that the positive verbal suggestion did not reduce perceived stress is most probably due to a floor effect, since stress at baseline was very low (see **Figure 2**). Finally, the consideration that anticipatory anxiety might have prevented the induction of a placebo effect suggests to additionally collect fear ratings during the course of the intervention.

Summarizing, this study was the first to investigate effects of positive and negative verbal suggestions in combination with the intravenous application of saline solution on cardiac parameters in patients with a history of TTC compared to controls. Only an increase of SBP could be observed as a response to both positive and negative suggestions. Secondly the increase of SBP as a response to the nocebo intervention was congruently accompanied by higher levels of SUD. The increase of HR prior to the beginning of the nocebo intervention is possibly associated to anticipatory anxiety of the nocebo intervention. Our hypothesis that the cardiac response towards placebo and nocebo interventions in patients with a history of TTC would be different from those of heart-healthy controls could not be confirmed with our data, a TTC, on average diagnosed two years ago, does not appear to have an influence on the responsivity to placebo resp. nocebo interventions. This becomes even more important considering the fact that the etiology of TTC is not yet fully explained. The assumption that an altered sympathetic disposition might build the precondition for the pathophysiological cascade of TTC-patient's myocardium within the acute phase, could not be verified with our placebo resp. nocebo interventions, at least at the time of our examination, on average, two years after the acute phase.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Code of Conduct of the Technical University Munich, Germany, with written informed consent

from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the institutional board of the Technical University Munich, Germany.

AUTHOR CONTRIBUTIONS

EO, KM, SS, GS, DS, AM, CB, HE, and JR designed the experiment. EO, SS, and DS performed the experiment. EO, KM, AM, DS, SB, K-HL and SH analyzed the data. EO drafted the first version of the manuscript. All authors interpreted the data and critically reviewed the manuscript.

FUNDING

The study was supported by the Deutsches Herzzentrum, Technische Universitaet, Munich, Germany. This work was supported by the German Research Foundation (DFG) and the Technical University of Munich within the funding program Open Access Publishing.

REFERENCES

1. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. *Pain* (2008) 136(1–2):211–8. doi: 10.1016/j.pain.2008.02.006
2. De Houwer J. A functional-cognitive perspective on the relation between conditioning and placebo research. *Int Rev Neurobiol* (2018) 138:95–111. doi: 10.1016/bs.irn.2018.01.007
3. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* (2003) 23(10):4315–23. doi: 10.1523/JNEUROSCI.23-10-04315.2003
4. Benedetti F. *Placebo effects,* 2nd ed. New York, NY, US: Oxford University Press (2014). doi: 10.1093/acprof:oso/9780198705086.001.0001
5. Aslaksen PM, Bystad M, Vambheim SM, Flaten MA. Gender differences in placebo analgesia: event-related potentials and emotional modulation. *Psychosom Med* (2011) 73(2):193–9. doi: 10.1097/PSY.0b013e3182080d73
6. Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain* (2013) 154(4):511–4. doi: 10.1016/j.pain.2013.02.002
7. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anesthesiology* (2007) 20(5):435–9. doi: 10.1097/ACO.0b013e3282b972fb
8. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* (2001) 293(5532):1164–6. doi: 10.1126/science.1060937
9. Benedetti F, Arduino C, Amanzio M. Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci* (1999) 19(9):3639–48. doi: 10.1523/JNEUROSCI.19-09-03639.1999
10. Meissner K. The placebo effect and the autonomic nervous system: evidence for an intimate relationship. *Philos Trans Royal Society B Biol Sci* (2011) 366(1572):1808–17. doi: 10.1098/rstb.2010.0403
11. Meissner K, Fässler M, Rücker G, Kleijnen J, Hróbjartsson A, Schneider A, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Internal Med* (2013) 173(21):1941–51. doi: 10.1001/jamainternmed.2013.10391
12. Ronel J, Mehilli J, Ladwig K-H, Blättler H, Oversohl N, Byrne RA, et al. Effects of verbal suggestion on coronary arteries: results of a randomized controlled experimental investigation during coronary angiography. *Am Heart J* (2011) 162(3):507–11. doi: 10.1016/j.ahj.2011.06.016
13. Amigo I, Cuesta V, Fernández A, González A. The effect of verbal instructions on blood pressure measurement. *J Hypertens* (1993) 11(3):293–6. doi: 10.1097/00004872-199303000-00010
14. El Mahmoud R, Mansencal N, Pilliere R, Leyer F, Abbou N, Michaud P, et al. Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. *Am Heart J* (2008) 156(3):543–8. doi: 10.1016/j.ahj.2008.05.002
15. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation* (2006) 113(14):1807–16. doi: 10.1161/CIRCULATIONAHA.106.174287
16. Kurisu S, Sato H, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: a novel cardiac syndrome mimicking acute myocardial infarction. *Am Heart J* (2002) 143(3):448–55. doi: 10.1067/mhj.2002.120403
17. Haghi D, Roehm S, Hamm K, Harder N, Suselbeck T, Borggrefe M, et al. Takotsubo cardiomyopathy is not due to plaque rupture: an intravascular ultrasound study. *Clin Cardiol* (2010) 33(5):307–10. doi: 10.1002/clc.20747
18. Medeiros K, O'Connor MJ, Baicu CF, Fitzgibbons TP, Shaw P, Tighe DA, et al. Systolic and diastolic mechanics in stress cardiomyopathy CLINICAL PERSPECTIVE. *Circulation* (2014) 129(16):1659.
19. Wittstein IS. The sympathetic nervous system in the pathogenesis of takotsubo syndrome. *Heart Failure Clinics* (2016) 12(4):485–98. doi: 10.1016/j.hfc.2016.06.012
20. Deshmukh A, Kumar G, Pant S, Rihal C, Murugiah K, Mehta JL. Prevalence of Takotsubo cardiomyopathy in the United States. *Am Heart J* (2012) 164(1):66–71 e1. doi: 10.1016/j.ahj.2012.03.020
21. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* (2006) 27(13):1523–9. doi: 10.1093/eurheartj/ehl032
22. Klinceva M, Widimsky P, Pesl L, Stasek J, Tousek F, Vambera M, et al. Prevalence of stress-induced myocardial stunning (Tako-Tsubo cardiomyopathy) among patients undergoing emergency coronary angiography for suspected acute myocardial infarction. *Int J Cardiol* (2007) 120(3):411–3. doi: 10.1016/j.ijcard.2006.07.228
23. Kurowski V, Kaiser A, von Hof K, Killermann DP, Mayer B, Hartmann F, et al. Apical and midventricular transient left ventricular dysfunction syndrome (tako-tsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* (2007) 132(3):809–16. doi: 10.1378/chest.07-0608
24. Parodi G, Del Pace S, Carrabba N, Salvadori C, Memisha G, Simonetti I, et al. Incidence, clinical findings, and outcome of women with left ventricular apical ballooning syndrome. *Am J Cardiol* (2007) 99(2):182–5. doi: 10.1016/j.amjcard.2006.07.080
25. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med* (2015) 373(10):929–38.
26. Ghadri JR, Sarcon A, Diekmann J, Bataiosu DR, Cammann VL, Jurisic S, et al. Happy heart syndrome: role of positive emotional stress in takotsubo syndrome. *Eur Heart J* (2016) 37(37):2823–9. doi: 10.1093/eurheartj/ehv757
27. Katsanos S, Filippatou A, Ruschitzka F, Filippatos G. Positive emotions and Takotsubo syndrome:'happy heart'or 'Diagoras' syndrome? *Eur Heart J* (2016) 37(37):2821–2. doi: 10.1093/eurheartj/ehw197
28. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, et al. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol* (2010) 55(4):333–41. doi: 10.1016/j.jacc.2009.08.057
29. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol* (2007) 50(5):448–52. doi: 10.1016/j.jacc.2007.03.050
30. Ghadri J-R, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on takotsubo syndrome (part I):

clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* (2018) 39(22):2032–46. doi: 10.1093/eurheartj/ehy076
31. Redfors B, Vedad R, Angeras O, Ramunddal T, Petursson P, Haraldsson I, et al. Mortality in takotsubo syndrome is similar to mortality in myocardial infarction - A report from the SWEDEHEART registry. *Int J Cardiol* (2015) 185:282–9. doi: 10.1016/j.ijcard.2015.03.162
32. Sobue Y, Watanabe E, Ichikawa T, Koshikawa M, Yamamoto M, Harada M, et al. Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate. *Int J Cardiol* (2017) 235:87–93. doi: 10.1016/j.ijcard.2017.02.090
33. Burgdorf C, Kurowski V, Bonnemeier H, Schunkert H, Radke PW. Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies. *Eur J Heart Fail* (2008) 10(10):1015–9. doi: 10.1016/j.ejheart.2008.07.008
34. Burgdorf C, Nef HM, Haghi D, Kurowski V, Radke PW. Tako-tsubo (stress-induced) cardiomyopathy and cancer. *Ann Intern Med* (2010) 152(12):830–1. doi: 10.7326/0003-4819-152-12-201006150-00026
35. Singh K, Carson K, Shah R, Sawhney G, Singh B, Parsaik A, et al. Meta-analysis of clinical correlates of acute mortality in takotsubo cardiomyopathy. *Am J Cardiol* (2014) 113(8):1420–8. doi: 10.1016/j.amjcard.2014.01.419
36. Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *Int J Cardiol* (2014) 174(3):696–701. doi: 10.1016/j.ijcard.2014.04.221
37. Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. *Herz* (2010) 35(4):240–3. doi: 10.1007/s00059-010-3339-x
38. Kresh JY, Izrailtyan I. Evolution in functional complexity of heart rate dynamics: a measure of cardiac allograft adaptability. *Am J Physiol* (1998) 275(3 Pt 2):R720–7. doi: 10.1152/ajpregu.1998.275.3.R720
39. Neumeister B, Böhm BO, Adler S. *Klinikleitfaden Labordiagnostik*. Elsevier Health Sciences (2018).
40. Katan M, Morgenthaler N, Widmer I, Puder JJ, Konig C, Muller B, et al. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. *Neuroendocrinology Letters* (2008) 29(3):341–6.
41. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. *Peptides* (2005) 26(12):2500–4. doi: 10.1016/j.peptides.2005.04.019
42. Widmer IE, Puder JJ, König C, Pargger H, Zerkowski HR, Girard Jr, et al. Cortisol response in relation to the severity of stress and illness. *J Clin Endocr Metabolism* (2005) 90(8):4579–86. doi: 10.1210/jc.2005-0354
43. Grelotti DJ, Kaptchuk TJ. *Placebo by proxy. BMJ (Clinical research ed.)* (2011) 343, d4345. doi:10.1136/bmj.d4345
44. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* (2007) 147(2):260–71. doi: 10.1016/j.neuroscience.2007.02.020
45. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *PAIN*® (2011) 152(7):1486–94. doi: 10.1016/j.pain.2011.01.043
46. van Laarhoven AI, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PC, Evers AW. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. *J Invest Dermatol* (2015) 135(5):1234–43. doi: 10.1038/jid.2014.522
47. Meissner K. *Placebo responses on cardiovascular, gastrointestinal, and respiratory organ functions*. In: *Placebo*., Berlin, Heidelberg: Springer (2014). p. 183–203. doi: 10.1007/978-3-662-44519-8_11
48. Agras SW, Horne M, Taylor BC. Expectation and the blood-pressure-lowering effects of relaxation. *Psychosom Med* (1982) 44(4):389–95. doi: 10.1097/00006842-198209000-00006
49. Zimmermann-Viehoff F, Meissner K, Koch J, Weber CS, Richter S, Deter HC. Autonomic effects of suggestive placebo interventions to increase or decrease blood pressure: a randomized controlled trial in healthy subjects. *J Psychosom Res* (2013) 75(1):32–5. doi: 10.1016/j.jpsychores.2013.03.011
50. Anderson ML. Neural reuse: a fundamental organizational principle of the brain. *Behav Brain Sci* (2010) 33(4):245–66. doi: 10.1017/S0140525X10000853
51. Lyby PS, Forsberg JT, Åsli O, Flaten MA. Induced fear reduces the effectiveness of a placebo intervention on pain. *PAIN*® (2012) 153(5):1114–21. doi: 10.1016/j.pain.2012.02.042
52. Ploghaus A, Tracey I, Clare S, Gati JS, Rawlins JNP, Matthews PM. Learning about pain: the neural substrate of the prediction error for aversive events. *Proc Natl Academy Sci* (2000) 97(16):9281–6. doi: 10.1073/pnas.160266497
53. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, et al. Does anticipation of pain affect cortical nociceptive systems? *J Neurosci* (2002) 22(8):3206–14. doi: 10.1523/JNEUROSCI.22-08-03206.2002
54. Wiech K, Ploner M, Tracey I. Neurocognitive aspects of pain perception. *Trends Cognit Sci* (2008) 12(8):306–13. doi: 10.1016/j.tics.2008.05.005
55. Ritter C, Hebart MN, Wolbers T, Bingel U. Representation of spatial information in key areas of the descending pain modulatory system. *J Neurosci* (2014) 34(13):4634–9. doi: 10.1523/JNEUROSCI.4342-13.2014
56. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia–imaging a shared neuronal network. *Science* (2002) 295(5560):1737–40. doi: 10.1126/science.1067176
57. Geuter S, Eippert F, Attar CH, Büchel C. Cortical and subcortical responses to high and low effective placebo treatments. *Neuroimage* (2013) 67:227–36. doi: 10.1016/j.neuroimage.2012.11.029
58. Watson A, El-Deredy W, Iannetti GD, Lloyd D, Tracey I, Vogt BA, et al. Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. *PAIN*® (2009) 145(1–2): 24–30. doi: 10.1016/j.pain.2009.04.003
59. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* (2004) 303(5661):1162–7. doi: 10.1126/science.1093065
60. Palermo S, Benedetti F, Costa T, Amanzio M. Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. *Human brain mapping* (2015) 36(5):1648–61. doi: 10.1002/hbm.22727
61. Johansen O, Brox J, Flaten MA. Placebo and nocebo responses, cortisol, and circulating beta-endorphin. *Psychosom Med* (2003) 65(5):786–90. doi: 10.1097/01.PSY.0000082626.56217.CF
62. Greenberg G, Haraway MM. *Comparative psychology: a handbook*. New York & London:Taylor & Francis (1998). doi: 10.4324/9780203826492
63. Meissner K, Enck P, Muth E, Kellermann S, Klosterhalfen S. Cortisol levels predict motion sickness tolerance in women but not in men. *Physiol Behav* (2009) 97(1):102–6. doi: 10.1016/j.physbeh.2009.02.007
64. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, et al. The magnitude of nocebo effects in pain: a meta-analysis. *PAIN*® (2014) 155(8):1426–34. doi: 10.1016/j.pain.2014.04.016
65. Vase L, Riley JL, III, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* (2002) 99(3):443–52. doi: 10.1016/S0304-3959(02)00205-1
66. Montgomery GH, Kirsch I. Classical conditioning and the placebo effect. *Pain* (1997) 72(1–2):107–13. doi: 10.1016/S0304-3959(97)00016-X
67. Wallström S, Ulin K, Määttä S, Omerovic E, Ekman I. Impact of long-term stress in Takotsubo syndrome: Experience of patients. *Eur J Cardiovasc Nurs* (2016) 15(7):522–8. doi: 10.1177/1474515115618568
68. Rosman L, Dunsiger S, Salmoirago-Blotcher E. Cumulative impact of stressful life events on the development of Takotsubo cardiomyopathy. *Ann Behav Med* (2017) 51(6):925–30. doi: 10.1007/s12160-017-9908-y
69. Lyon A. Stress in a dish. *Explor Mech Takotsubo Syndrome* (2017) 70(8):992–5. doi: 10.1016/j.jacc.2017.07.716
70. Borchert T, Hubscher D, Guessoum CI, Lam TD, Ghadri JR, Schellinger IN, et al. Catecholamine-dependent beta-adrenergic signaling in a pluripotent stem cell model of takotsubo cardiomyopathy. *J Am Coll Cardiol.* (2017) 70(8):975–91. doi: 10.1016/j.jacc.2017.06.061

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7 Paper II

PSYCHOLOGY, HEALTH & MEDICINE
https://doi.org/10.1080/13548506.2020.1722315

Taylor & Francis
Taylor & Francis Group

Psychosocial and physical long-term outcome in patients with a history of takotsubo cardiomyopathy or myocardial infarction - a multi-centered case control study

E. Olliges[a,b], C. Burgdorf[c], K.H. Ladwig[d,e], C. Moeller[f], D. Deftu-Kloes[g], S. Pohl[h], B. Ruettner[i], G. Richardt[j], K. Meissner[a,b], A. Steger[k], L. Goetzmann[g] and J. Ronel[l,d]

[a]Institute of Medical Psychology, Faculty of Medicine, LMU Munich, Munich, Germany; [b]Division of Health Promotion, Coburg University of Applied Sciences, Coburg, Germany; [c]Department of Cardiology, Heart and Vascular Centre Bad Bevensen, Bad Bevensen, Germany; [d]Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Techni- sche Universitaet Muenchen, Munich, Germany; [e]Department of Epidemiology II, Helmholtz Zentrum, Munich, Germany; [f]Medical Clinic II, Luebeck, Universitaetsklinikum Schleswig-Holstein, Germany; [g]Department of Psychosomatic Medicine and Psychotherapy, Segeberger Kliniken, Bad Seg- eberg, Germany; [h]Psychiatric Day-care Hospital, Klinikum Frankfurt (Oder), Frankfurt Oder, Germany; [i]Department of Psychology, Medical School Hamburg, Germany; [j]Department of Cardiology, Segeberger Kliniken, Bad Segeberg, Germany; [k]Klinik und Poliklinik fuer Innere Medizin I, Klinikum rechts der Isar, Technische Universitaet Muenchen, Munich, Germany; [l]Department of Psychosomatic Medicine and Psychotherapy, Klinik Barmelweid AG, Barmel- weid, Switzerland

ABSTRACT

Physical long-term impacts of Takotsubo Cardiomyopathy (TTC) remain controversial and an underestimation of their severity becomes increasingly evident. Even less is known about mental long-term impacts of TTC. This study aims at a better understanding of the physical and mental long-term effects of TTC in comparison to myocardial infarctions (MI).

On average 5 years after disease onset, 68 TTC patients and 68 age- and sex-matched MI patients were assessed for disease-related quality of life, depression, anxiety, chronic stress, social support, resilience, and life events prior to disease onset. Scores of TTC and MI patients were compared to each other and to normative references values. Regression analyses were used to evaluate the predictive value of the number of life events prior to disease onset for physical and mental long-term outcomes.

Both groups displayed higher scores in depression and anxiety, higher levels of chronic stress, and lower scores in physical and mental quality of life in comparison to norm samples, while social support did not differ from norms. No differences between the two patient groups were observed. Within both groups, the majority of patients (TTC: 69.1%; MI: 60.3%) reported stressful life events prior to disease onset. In TTCs and MIs, the number of events had a significant impact on long-term mental health and chronic stress. Notably, both patient collectives scored higher in resilience than healthy controls.

Results suggest negative long-term impacts of TTC on mental and physical wellbeing, comparable to those of MI. Besides a good

ARTICLE HISTORY
Received 3 May 2019
Accepted 25 December 2019

KEYWORDS
Takotsubo cardiomyopathy; myocardial infarction; disease outcome; anxiety; depression; stress; quality of life; resilience; coping strategies

CONTACT E. Olliges Elisabeth.Olliges@med.uni-muenchen.de Institute of Medical Psychology, Faculty of Medicine, LMU Munich, Goethestr. 31, Munich 80336, Germany

somatic-medical care, psychotherapeutic support, including the development of functional coping strategies, might be warranted for TTC patients. The long-term impact of TTC should be taken as serious as that of MI.

Introduction

The Takotsubo Cardiomyopathy (TTC; also termed 'Stress-induced cardiomyopathy', 'Broken- Heart Syndrome') is considered as rare, reversible, and acquired form of primary myocardial disorders. After its first description in Japan in 1990, TTC became increasingly acknowledged and gained worldwide recognition (Kurisu et al., 2002; Kurowski et al., 2007; Parodi et al., 2007; Sato, 1990). TTC is characterized by an acute functional disturbance in the contraction of the myocardium, primarily affecting mid and apical areas of the left ventricle. The modified shape of the left ventricle at the end of the systole (visualized by means of angiographic examinations) evokes the form of a Japanese octopus trap, termed 'Tako-Tsubo'. Data on the prevalence of TTC vary (Deshmukh et al., 2012; Maron et al., 2006). Approximately 0.07–3% of patients with suspected Acute Coronary Syndrome (ACS), are diagnosed with TTC after cardiac catheter examination. Nearly 90% of all TTC patients are postmenopausal women. Hormones (e.g. estrogen) seem to function as protection factors, but currently, it is unclear, why women are more prone to develop TTC (Grodstein and Stampfer, 1995). The clinical presentation of TTC and MI is often similar. Both patient groups are mostly reporting sudden chest pain and pronounced dyspnea, accompanied by electrocardiogram alterations, and an increase in cardiac biomarkers. Hence, TTC can only be distinguished from MI via heart catheter examination (Ghadri, Wittstein, et al., 2018; Klinceva et al., 2007; Kurowski et al., 2007; El Mahmoud et al., 2015; Parodi et al., 2007; Schofer et al., 2014; Wedekind, Möller, & Scholz, 2006). Coronary arteries are mostly unaffected in TTC patients. However, coronary artery disease (CAD) can simultaneously exist (Haghi et al., 2010; Templin et al., 2015).

From a psychophysiological perspective, an excessive activation of the sympathetic nervous system is discussed to be a major factor for the development of TTC and several studies suggest that elevated catecholamine concentrations function as mediating mechanism (Borchert et al., 2017; Wittstein, 2016; Frustaci et al., 1991, Khullar et al., 1989).. Nonetheless, the etiology of TTC remains unclear. Acute emotionally or physical stressful events prior to the onset of the disease could be identified in approximately 70% of TTC patients, whereas research on chronic stress in TTC remains limited (Delmas et al., 2013; Summers, Lennon, & Prasad, 2010; Templin et al., 2015).

Based on the observation of a rapid normalization of the systolic left-ventricular ejection fraction (LVEF) and regional wall motion after the acute phase, TTC is usually considered a benign, reversible disorder (Elesber et al., 2007; Pilgrim & Wyss, 2008; Schneider et al., 2010). However, data on long-term follow-ups are sparse and ambivalent (Khalighi, Farooq, Aung, & Oo, 2015). Whilst survival rates have been found not to differ from those of an age- and sex-matched population (Elesber et al., 2007; Ghadri, Kato et al., 2018, Ghadri, Wittstein et al., 2018; Valbusa et al., 2008), several studies described similar early and late mortality in TTC patients compared to patients after MI and

a significantly higher mortality rate in comparison with a control group of the same age and sex (Ghadri, Kato et al., 2018; Redfors et al., 2015; Sobue et al., 2017; Templin et al., 2015). Apart from cardiovascular events, this appears to be due to an increased prevalence of non-cardiac comorbidities, especially cancer (Burgdorf, Kurowski, Bonnemeier, Schunkert, & Radke, 2008; Burgdorf, Nef, Haghi, Kurowski, & Radke, 2010; Sharkey et al., 2010; Singh et al., 2014). Furthermore, recent studies indicate that TTC may have long-lasting negative cardiac consequences in terms of persistent heart failure symptoms, worse than previously reported (Ionescu, Aguilar-Lopez, Sakr, Ghantous, & Donohue, 2010; Scally et al., 2018).

First studies examined the question of whether the type of trigger (e.g. emotional or physical) is associated with short term disease outcome. Again, results represent a high variability. Higher age and the occurrence of emotional (e.g. workplace problems or loss of a relative) seem to predict more favorable outcomes, instead of physical events (e.g. infections or surgeries) (Templin et al., 2015). Further, sex appears to play a crucial role; negative endpoints, such as in-hospital death occurred more often among men (Sobue et al., 2017; Templin et al., 2015). Compare et al., however, reported that type of trigger made no differences in quality of life (QoL) and emotional burden one year after disease onset (Compare et al., 2014).

Contrary to the field of cardiovascular disease (CVD), research on risk and protection factors as well comorbidities in TTC patients is less advanced (Freedland, 2017; Freedland et al., 2003; Ladwig et al., 2017, 2013). Psychosocial risk factors, for instance stressful life events (e.g. loss of a relative or financial stress) and especially chronic stress, as well as anxiety and depression are highly associated with an increased risk for the development of CVD and an unfavorable disease progression (Dimsdale, 2008; Miller et al., 2002; Mostofsky et al., 2012; Penninx, 2017; Rosengren et al., 2004). Simultaneously, social support and resilience, as the individual's salutogenic ability to functionally respond to, and integrate specific negative conditions or life crises, have emerged to serve as protection factors (Barth, Schneider, & Von Känel, 2010). First studies also indicate higher levels of depressive and anxiety symptoms as well as increased distress in patients with a history of TTC (Compare et al., 2014; Mudd, Kapur, Champion, Schulman, & Wittstein, 2007; Nguyen et al., 2009; Salmoirago-Blotcher et al., 2016; Smeijers, Szabo, & Kop, 2016; Smeijers et al., 2015; Summers et al., 2010). Finally, an extensive cardiologic cohort study with 1750 TTC patients (89.9% female) showed that patients with TTC present a higher prevalence of former or chronic neurologic or psychiatric disorders (Templin et al., 2015). However, long-term effects of TTC on mental well-being and QoL have not yet been examined.

Against this ambiguous background, this study aimed at a better understanding of the long-term impacts of TTC on patients' mental and physical QoL in comparison to patients with a history of MI as well as to normal reference values. In a cross-sectional approach, 68 patients with a history of TTC and MI, respectively, filled in a comprehensive catalogue of standardized questionnaires capturing concurrent QoL, depression, anxiety, chronic stress, social support and resilience scores. Due to more recent randomized-controlled trials, arguing an underestimation of the severity of TTC, we hypothesized that psychosocial and physical long-term outcomes in patients with a history of TTC are at least similar to those of MI, we also examined the predictive value of the amount of stress events prior to

disease onset for long-term outcomes in psychosocial and physical variables (Ionescu et al., 2010; Scally et al., 2018).

Methods

Within this multi-centered, case-control study biographical, psychosocial and physical characteristics of TTC and MI patients were examined by means of a postal survey. Data from these questionnaires was complemented with cardiac markers and disease classifications at disease onset (LVEF, creatine kinase (muscle/brain) (CK, CK-MB), New York Heart Association Functional Classification (NYHA)), which were collected from the local databases. The study protocol followed the principles of GCP/Helsinki and was approved by the corresponding institutional review boards (Technische Universitaet, Munich, Universitaet zu Luebeck).

Sample

The total sample of 136 patients comprised 68 patients diagnosed with TTC and 68 post MI patients who received diagnostics and treatment in the cardiological departments Deutsches Herzzentrum and Klinikum Rechts der Isar, Technische Universitaet, Munich, as well as Segeberger Kliniken and Medizinische Klink II, Universitaetsklinikum Schleswig-Holstein, Campus Luebeck (see Table 1). TTC and MI patients were matched according to age and sex.

Table 1. Sample characteristics.

	TTC (n = 68)	MI (n = 68)	*p*
Center			.2††
Deutsches Herzzentrum, Technische Universitaet, Munich, *n*	21	22	
Klinikum rechts der Isar, Technische Universitaet, Munich, *n*	9	12	
Bad Segeberger Kliniken, *n*	10	16	
Medizinische Klinik II, Universitaetsklinkum Schleswig-Holstein, Campus Luebeck, *n*	28	18	
Age, *Mean (SD), years*	68.3 (11.8)	69.2 (10.6)	.65†
Sex, *n* (male/female)	4/64	4/64	
Number of children, *Median (IQR)*	2 (1)	2 (2)	.79 ††
Current living situation (multiple answers possible)			
Living alone, *n*	22	23	.86†††
With a partner, *n*	42	41	.86†††
With children, *n*	15	12	.68 †††
In a shared apartment, *n*	1	0	.31†††
With parents/parents in law	1	0	1.0†††
Current working situation			
full-time, *n*	6	5	
part-time, *n*	3	6	
unemployed, *n*	2	2	
incapacitated for work, *n*	1	3	
within the own household, *n*	15	7	
retired,	30	29	
others, *n*	5	2	.63††
Time span since diagnosis *Mean (SD), months*	58.32 (27.37)	49.92 (28,99)	.07†††

Note: Due to their epidemiological characteristics, the average age of the total sample was relatively high (M = 68.7 years). As to be expected, the female sex prevails (94%).
† T-Test †† Chi-square-Test ††† Mann-Whitney-Test

Inclusion criteria

TTC patients were considered for participation if they fulfilled the Mayo Clinic's diagnostic criteria for stress-induced cardiomyopathy, as follows: (1) transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities extending beyond a single epicardial vascular distribution with a stressful trigger often, but not always, present. (2) Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. (3) New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin. (4) Absence of a pheochromocytoma or myocarditis (Madhavan & Prasad, 2010).

In conformity with the American Heart Association, the inclusion criteria for MI patients were as follows: (1) Symptoms of myocardial ischemia (2) new ischemic ECG changes, (3) development of pathological Q waves (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology (5) identification of a coronary thrombus by angiography or autopsy (Schofer et al., 2014; Thygesen et al., 2018).

Procedure

Patients with a history of TTC or MI, who met all inclusion criteria and none of the exclusion criteria, were identified within local databases through the local study personnel. Both patient groups were matched according to age and sex. All data was de-identified with codes only available to the study coordinator. Potentially eligible patients were called, informed about the purpose of the study, and asked for permission to send the survey battery, containing 10 standardized, validated questionnaires (only 6 reported here; for other questionnaires, see Goetzmann et al., submitted). Non-responders were called again and reminded to complete the questionnaire after 4 weeks.

Measures

Disease-related QoL was assessed by using the short form (SF-12) questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ). The SF-12 is a validated and internationally established questionnaire, examining physical and mental related QoL (PCS/MCS) during the preceding 4 weeks, while KCCQ serves as a self-assessment tool to measure heart-failure-specific QoL. It consists of 23 items, rating six domains (e.g. physical restrictions, symptom frequency, social restrictions, self-efficacy, or QoL). These domains are summarized into the subscales functional status and clinical summary. Both tools fulfil the criteria for test quality with an internal consistency of Cronbachs $\alpha = .8$ for SF-12, respectively Cronbachs $\alpha = .93$ for KCCQ (Bullinger, 2000; Faller et al., 2005; Green, Porter, Bresnahan, & Spertus, 2000; Lim & Fisher, 1999; Müller-Nordhorn, Roll, & Willich, 2004; Resnick & Parker, 2001; Ware, Kosinski, & Keller, 1996). Presence of depression and/or anxiety was assessed by means of the Patients Health Questionnaire (PHQ-4). The ultra-brief, but reliable and valid version of the PHQ-4, that examines depression and anxiety with four items in accordance with the Diagnostic and Statistical Manual of Mental Disorders (Khubchandani, Brey, Kotecki, Kleinfelder, & Anderson, 2016; Kroenke,

Spitzer, Williams, & Lowe, 2009; Michal et al., 2015; Vahia, 2013). Stress within the previous three months was evaluated by using the 'Screening Scale for Unspecific Chronic Stress' (SSCS) as obtained from the 'Trier Inventory for Chronic Stress' (TICS). It's internal consistency (Cronbachs α of .91) and reliability (.84 – .91) is considered very good (Petrowski, Paul, Albani, & Brähler, 2012; Schulz & Schlotz, 1999). The 'Resilience Scale' (RS-5) was used as a validated tool to measure resilience, as the individual's salutogenic ability, with 5 items. 'RS-5' was psychometrically reviewed with an internal consistency of Cronbachs α = .80 (Schmalbach et al., 2016; Wagnild & Young, 1993). Finally, the ENRICHD Social Support Instrument (ESSI) served as a validated tool to quantify social support (Cordes, Herrmann-Lingen, Büchner, & Hessel, 2009; Kendel et al., 2011; Roest et al., 2013).

Furthermore, the following socio-demographic characteristics were also collected: number of children, housing situation, and current working situation (see Table 1).

Statistical analysis

All statistical analyses were performed by means of IBM SPSS Statistics 25, with a p-value ≤ 0.05 indicating statistical significance. To investigate possible differences between TTCs, MIs and norms, Bonferroni-corrected independent samples T-Tests were performed for normally distributed, continuous variables; Mann-Whitney-U Tests for non-normally distributed, continuous variables, and Chi-square tests for categorical variables. Separate linear regression analyses were performed to investigate whether the variance in psychosocial variables (i.e. disease related QoL, depression and anxiety, chronic stress, social support and resilience) at survey time could be explained by the number of life events before disease onset (see Table 3).

Results

Sample characteristics

Both patient collectives were comparable in regard to age, sex, (male = 8) and further socio- demographic characteristics (see Table 1). Mean time span since diagnosis was 58.32 months, SD = 27.37 in TTCs and 49.92 months, SD = 28.99 in MIs (p = .07). Within both groups more than half of the patients reported a stressful life event prior to their disease (TTC: 69.1%; MI: 60.3%) (see Table 1).

As indicated in Table 2, post TTC and MI patients scored lower than norms in both the mental and physical SF-12 subscales (p's< 0.05), while no significant differences between the two patient groups emerged (Nübling, Andersen, & Mühlbacher, 2006). Similarly, heart-failure-specific QoL (KCCQ) was significantly lower in TTC patients and post MI patients as compared to norms (p's< 0.05) (Faller et al., 2005). Again, there was no difference between the two patient groups detected. Furthermore, anxiety and depression scores (PHQ-4) were significantly higher in both patient collectives than in norm samples (p's< 0.05) (Lowe et al., 2010). Again, no differences could be observed between the two patient collectives. In addition, patients with a history of TTC or MI did not differ with regard to chronic stress (SSCS – TICS) but reported significantly higher chronic stress scores than the norm sample (p's< 0.05) (Schulz & Schlotz, 1999). Interestingly, resilience

Table 2. Comparison between TTC, MI, and norm values.

	TTC		MI		TTC vs. MI	Norm		TTC vs. Norm	MI vs. Norm
	M	*SD*	*M*	*SD*	*p**	*M*	*SD*	*p**	*p**
SF-12									
SF-12-PCS	47.23	11.91	46.81	11.58	.99	50	10	≤ .05	≤ .05
SF-12-MCS	41.55	17.21	43.47	16.2	.75	50	10	≤ .05	≤ .05
KCCQ									
'functional status score'	45.1	9.5	45.17	9.87	.33	87	12	≤ .05	≤ .05
'clinical summary score'	68.56	11.97	67.59	9.43	.47	80	15	≤ .05	≤ .05
PHQ-4									
'anxiety'	1.94	1.6	1.56	1.6	.06 ††	.94	1.52		
'depression'	1.77	1.52	1.3	1.39	.09 ††	.82	1.1		
PHQ-4 sum	3.71	2.94	2.85	2.79	0.1	1.76	2.06	≤ .05	≤ .05
RS-5	28.63	5.42	29.8	5.61	.13	27.20	5.2	≤ .05	≤ .05
TICS-SSCS	57.5	16.53	53.14	15.34	.11	50	10	≤ .05	≤ .05
ESSI	21.51	3.28	21.02	4.30	.9	20.47	4.05	1.0	1.0

Note: Norm values have been withdrawn from standardized validation studies; since the PHQ-4 sub scores are not normally distributed, a statistical comparison to the norm sample was not indicated.

Abbreviations: SF-12, Short Form-12; SF-12-PCS, Short Form-12 Physical Component Score, SF-12-MCS, Short Form-12 Mental Component Score, KCCQ, Kansas City Cardiomyopathy Questionnaire; PHQ-4, Patient Health Questionnaire; RS-5, Resilience Scale-5; TICS-SSCS, Trier Inventory for Chronic Stress-Screening Scale for Unspecific Chronic Stress; ESSI, ENRICHD Social Support Instrument.

* Bonferroni-corrected *t*-Test

†† Mann-Whitney-Test

values (RS-5), were significantly higher in TTC and MI patients as compared to normative values (p's< 0.05), while again, resilience scores did not differ between the two patient groups (Schmalbach et al., 2016). Regarding social support (ESSI), no significant

Table 3. Physical parameter during acute phase and reported life events prior to the onset of the disease.

		TTC n (%)	MI n (%)	p-value
Physical parameters during acute phase				
Chest pain (%)		66.1	93.75	.00 ††
NYHA Stage (%)				1.6††
	I	45.6	50.00	
	II	15.8	17.4	
	III	15.8	17.4	
	IV	15.8	13.00	
LVEF (%)				1.6††
	< 30%	6.8	8	
	30–50%	83.1	50	
	> 50%	11.67	42.0	
CK (U/l) Mean (SD)		288.42 (442.46)	667.1 (911,06)	.00†††
CK-MB (U/l) Mean (SD)		47.65 (50.03)	94.34 (94.5)	.00†††
Life events prior to the onset of the disease				
Recall of life event, *n (%)*		47 (69.1%)	41 (60%)	.25†
Amount of life events Median (IQR)		1 (1.25)	1 (2)	.44††
Occupational stress		15 (22.1%)	18 (26.5%)	.73††
Conflicts at work		4 (5.9%)	5 (7.4%)	.35††
Stress within the family		19 (27.9%)	23 (33.8%)	.66††
Conflicts within the family		16 (23.5%)	9 (13.2%)	.02††
Strong, positive experiences		2 (2.9%)	5 (7.4%)	.68††
Strong, annoying experiences		11 (16.2%)	18 (26.5%)	.76††
Strong, joyful experiences		3 (4.4%)	8 (11.8%)	.68††
Cases of death within the immediate surroundings		9 (12.9%)	10 (14.3%)	.93††
Further life events		17 (24.3%)	12 (17.1%)	.9††

Abbreviations: NYHA, New York Heart Association; LVEF, left-ventricular ejection fraction; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain.

† T-Test

†† Chi-square-Test ††† Mann-Whitney-Test

Table 4. Linear regression analysis for the predictor 'number of life events'.

	b		SE		β		p-value	
Criterion variable	TTC	MI	TTC	MI	TTC	MI	TTC	MI
SF-12								
SF-12-PCS	.00	.05	1.2	1.1	.06	−.22	.67	.13
SF-12-MCS	.09	.12	1.43	.99	−.3	−.35	.03	.01
KCCQ								
'functional status score'	.00	.01	1.38	1.1	−.02	−.1	.89	.45
'clinical summary score'	.0	.05	2.29	1.51	.02	−.21	.89	.13
PHQ-4 sum score	.03	.11	.3	.24	.17	.33	.19	.01
RS-5	.02	.02	.54	.5	−.14	−.13	.26	.31
TICS-SSCS	.20	.08	.96	.84	.45	.29	.00	.02
ESSI	.09	.02	.32	.38	−.3	−.14	.02	.27

Abbreviations: SE, Standard Error; SF-12, Short Form-12; SF-12-PCS, Short Form-12 Physical Component Score, SF-12-MCS, Short Form-12 Mental Component Score, KCCQ, Kansas City Cardiomyopathy Questionnaire; PHQ-4, Patient Health Questionnaire-4; RS-5, Resilience Scale-5; TICS-SSCS, Trier Inventory for Chronic Stress-Screening Scale for Unspecific Chronic Stress; ESSI, ENRICHD Social Support Instrument

differences were observed, neither between patient groups nor between patients and norms (Cordes et al., 2009).

A majority of patients recalled the occurrence of life events prior to disease onset (TTC: 69.1%, MI: 60%). Both positive and negative events were reported, mainly referring to the areas family and occupation. Significant differences between TTCs and MIs could only be found for one response option (p = .02); TTCs reported almost twice as often 'conflicts within the family' prior to disease admission (Table 3).

Explorative linear regression analyses were performed to investigate whether the number of life events prior to disease onset has an influence on the collected psychosocial variables. In TTCs and MIs the number of life events significantly predicted SF-12-MCS and TICS-SSCS scores. Additionally, the number of life events significantly predicted ESSI scores in TTCs and PHQ-4 sum scores in MIs, respectively (see Table 4).

Discussion

This study aimed at a better understanding in psychosocial and physical long-term outcome of TTC patients in comparison to MI patients. Furthermore, both patient groups were compared to those of normative reference values. Within both patient groups, the history of a heart disease, be it TTC or MI, was associated with decreased physical (SF-12-PCS, KCCQ) and mental (SF-12-MCS, TICS-SSCS) QoL, as compared to norm samples. KCCQ summary scores of both patient groups were equivalent to those of MI patients with a LVEF lower than 40%, which implies a considerable restriction of the cardiac function (Pettersen, Kvan, Rollag, Stavem, & Reikvam, 2008). Also, the anxiety and depression sum score (PHQ-4) was significantly increased in both patient groups as compared to normative values, indicating mild symptoms (Kroenke et al., 2009). Therefore, our findings support the results of recent studies suggesting that patients with a history of TTC and MI are, faced with severe negative long-term mental and physical effects (Compare et al., 2014; Scally et al., 2018; Templin et al., 2015).

A bi-directional association between depressive symptoms and CAD is well established and first studies indicate a related link for TTCs. Further studies reported that the

relationship between depression and MIs might be even stronger in female patients than it is for males (Doyle et al., 2015; Naqvi, Naqvi, & Merz, 2005). A similar association could also be conceivable for TTC patients. Considering the sex distribution within the present sample, this would give a hint to the decreased mental QoL in MIs as well as in TTCs, compared to norm samples. Notably, not only the majority of TTC patients (69.1%), but also 60% of MI patients were recalled stressful life events prior to disease onset. Additionally, to acute stressors prior to disease onset, also higher levels of chronic stress (TICS-SSCS) could be detected in patients with TTC as well as in post MI patients, compared to norm samples. Chronic stress includes the perception, appraisal, and response to repetitive, emotionally or physiologically challenging events or stimuli (Lazarus, 2006; McEwen, 2007). Gender differences in coping strategies (e.g. problem or emotion focused) for repetitive challenges have been described, with women being more likely to use emotional coping strategies and beyond that, tend to appraise stressors as more severe as men (Diehl, Coyle, & Labouvie-Vief, 1996; Sieverding, Kendel, & Böhmer, 2004; Tamres, Janicki, & Helgeson, 2002). This gains importance, because 96% of our sample were female patients and interestingly, only the stressor 'conflicts within the family' was reported more frequently in TTCs (see Table 3).

Since TTC is associated with an excessive activation of the sympathetic nervous system, differences in coping strategies and problem perception might help to explain the higher prevalence of TTC in women. Remarkably, the number of life events prior to disease onset was significantly related to perceived chronic stress and mental QoL in both patient collectives. Recent studies reported that especially the exposure to repeated stressful life events was related to the onset of TTC (Rosman, Dunsiger, & Salmoirago-Blotcher, 2017; Wallström, Ulin, Määttä, Omerovic, & Ekman, 2016). Authors argue that long-term stressful conditions might have led to an increased vulnerability to further emotional or physical stressors that in turn triggered the development of TTC. This suggests that the amount of life events might not only be a risk factor for the appearance of TTC, but also for long-term mental well-being. Therefore, maladaptive coping may not only contribute to the development of the heart disease but also to the impaired QoL many years after disease admission, as observed in our study. Further, the patients' perception of disease severity within the acute phase of TTC due to frightening symptoms, mimicking an acute coronary syndrome, could also be considered as a potential source of maladaptive coping. This explicitly fearsome perception of stress could be meaningful for the mental wellbeing of MIs and TTCs, also in the long-term.

Both patient groups displayed similar but significantly higher-than-normal scores of resilience. At a first glance, these results appear to be counterintuitive: Resilience, generally conceived as personality trait, would rather be considered a protection factor for the development of TTC and MI. A possible explanation could be the phenomenon of 'post-traumatic growth', defined as positive personal change through the experience of a striking traumatic or adverse life event (Cordova & Andrykowski, 2003; O'Leary & Ickovics, 1995; Roebuck, Furze, & Thompson, 2001).

The following limitations of our study need to be considered. Even though sex distribution of TTC patients (96% females) reflects sex distribution within the TTC population, the high proportion of female patients may have introduced some bias when comparing the results to 'equally sex distributed' normative values (Templin et al., 2015).

This might, be the case regarding the comparison of depression scores of our mostly female patient collectives and norm samples, because the prevalence of depression is higher among women than men, with a risk ratio of approximately 2:1 (Kessler, 2003). Furthermore, the over-representation of (elderly) female patients diminishes the generalizability to MI patients, who are predominantly male. Given the high variability of outcomes (see Table 3), which is in line with previous studies, a larger number of male and female participants would have been desirable in order to enhance the statistical power for the analyses (Compare et al., 2014; Rosman et al., 2017; Sobue et al., 2017). Considering the low TTC prevalence of only 0.07–3% in patients presenting with an acute coronary syndrome, however, the sample size of 68 TTC patients is comparably high and four study centers were necessary to retrieve these numbers in a reasonable time frame. In addition, matching was done for age and sex, but not for the time point of diagnosis. However, the time span between diagnosis and survey participation did not differ significantly between groups ($p = .07$). Nonetheless, the large variety of time periods between disease onset and the present survey may have had an impact on the individuals' answers; for example, a recall bias could have influenced the list of stress events prior to disease onset. Therefore, prospective studies are warranted to further consolidate our findings. Finally, due to the cross-sectional design of this study, baseline values of psychosocial variables as well as physiological risk factors (such as hypertension or diabetes) before and at disease onset were not available. Therefore, the possible impact of mental and physical conditions prior to the disease onset and the impact of the disease itself cannot be differentiated, and causal relationships cannot be drawn.

In summary, it can be concluded that patients with a history of TTC showed considerably reduced emotional and physical wellbeing on average 4.9 years after disease onset, which is comparable to that of MIs (Roebuck et al., 2001). Both patient groups, TTC and MI, reported higher chronic stress levels as well as reduced health related QoL. Whether this is associated with maladaptive coping strategies in regard to potential life stressors needs to be tested in further studies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

E. Olliges http://orcid.org/0000-0002-5485-3354

References

Barth, J., Schneider, S., & Von Känel, R. (2010). Lack of social support in the etiology and the prognosis of coronary heart disease: A systematic review and meta-analysis. *Psychosomatic Medicine*, *72*(3), 229–238.

Borchert, T., Hubscher, D., Guessoum, C. I., Lam, T. D., Ghadri, J. R., Schellinger, I. N., & Streckfuss-Bömeke, K. (2017). Catecholamine-dependent beta-adrenergic signaling in a pluripotent stem cell model of takotsubo cardiomyopathy. *Journal of the American College of Cardiology*, *70*(8), 975–991.

Bullinger, M. (2000). Erfassung der gesundheitsbezogenen Lebensqualität mit dem SF-36-Health Survey. [journal article]. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz*, *43*(3), 190–197.

Burgdorf, C., Kurowski, V., Bonnemeier, H., Schunkert, H., & Radke, P. W. (2008). Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): Focus on malignancies. *European Journal of Heart Failure*, *10*(10), 1015–1019.

Burgdorf, C., Nef, H. M., Haghi, D., Kurowski, V., & Radke, P. W. (2010). Tako-tsubo (stress-induced) cardiomyopathy and cancer. *Annals of Internal Medicine*, *152*(12), 830–831.

Compare, A., Grossi, E., Bigi, R., Proietti, R., Shonin, E., Orrego, P. S., & Poole, L. (2014). Stress-induced cardiomyopathy and psychological wellbeing 1 year after an acute event. *Journal of Clinical Psychology in Medical Settings*, *21*(1), 81–91.

Cordes, A., Herrmann-Lingen, C., Büchner, B., & Hessel, A. (2009). Repräsentative Normierung des ENRICHD-Social-Support-Instrument (ESSI)-Deutsche Version. Klinische Diagnostik und Evaluation, 2(1), 16-32.

Cordova, M. J., & Andrykowski, M. A. (2003). Responses to cancer diagnosis and treatment: Posttraumatic stress and posttraumatic growth. *Seminars in Clinical Neuropsychiatry*, *8*(4), 286–296.

Delmas, C., Lairez, O., Mulin, E., Delmas, T., Boudou, N., Dumonteil, N., … Carrié, D. (2013). Anxiodepressive disorders and chronic psychological stress are associated with Tako-Tsubo cardiomyopathy. *Circulation Journal*, *77*(1), 175–180.

Deshmukh, A., Kumar, G., Pant, S., Rihal, C., Murugiah, K., & Mehta, J. L. (2012). Prevalence of Takotsubo cardiomyopathy in the United States. *American Heart Journal*, *164*(1), 66–71 e61.

Diehl, M., Coyle, N., & Labouvie-Vief, G. (1996). Age and sex differences in strategies of coping and defense across the life span. *Psychology and Aging*, *11*(1), 127.

Dimsdale, J. E. (2008). Psychological stress and cardiovascular disease. *Journal of the American College of Cardiology*, *51*(13), 1237–1246.

Doyle, F., McGee, H., Conroy, R., Conradi, H. J., Meijer, A., Steeds, R., … de Jonge, P. (2015). Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: A MINDMAPS study. *Psychosomatic Medicine*, *77*(4), 419–428.

El Mahmoud, R., Mansencal, N., Pilliere, R., Leyer, F., Abbou, N., Michaud, P., & Dubourg, O. (2008). Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. *American Heart Journal*, *156*(3), 543–548.

Elesber, A. A., Prasad, A., Lennon, R. J., Wright, R. S., Lerman, A., & Rihal, C. S. (2007). Four-year recurrence rate and prognosis of the apical ballooning syndrome. *Journal of the American College of Cardiology*, *50*(5), 448–452.

Faller, H., Steinbüchel, T., Schowalter, M., Spertus, J. A., Störk, S., & Angermann, C. E. (2005). Der Kansas City Cardiomyopathy Questionnaire (KCCQ) - ein neues krankheitsspezifisches Messinstrument zur Erfassung der Lebensqualität bei chronischer Herzinsuffizienz. [The Kansas City Cardiomyopathy Questionnaire (KCCQ) - A New Disease-Specific Quality of Life Measure for Patients with Chronic Heart Failure]. *Psychother Psych Med*, *55*(03/04), 200–208.

Freedland, K. E. (2017). A new era for Health Psychology. *Health Psychology*, *36*(1), 1–4.

Freedland, K. E., Rich, M. W., Skala, J. A., Carney, R. M., Davila-Roman, V. G., & Jaffe, A. S. (2003). Prevalence of depression in hospitalized patients with congestive heart failure. *Psychosomatic Medicine*, *65*(1), 119–128.

Frustaci, A., Loperfido, F., Gentiloni, N., Caldarulo, M., Morgante, E., & Russo, M. A. (1991). Catecholamine-induced cardiomyopathy in multiple endocrine neoplasia. A histologic, ultrastructural, and biochemical study. *Chest*, *99*(2), 382–385.

Ghadri, J. R., Kato, K., Cammann, V. L., Gili, S., Jurisic, S., Di Vece, D., … Templin, C. (2018). Long-term prognosis of patients with Takotsubo syndrome. *Journal of the American College of Cardiology*, *72*(8), 874–882.

Ghadri, J.-R., Wittstein, I. S., Prasad, A., Sharkey, S., Dote, K., Akashi, Y. J., … Templin, C. (2018). International expert consensus document on takotsubo syndrome (part I): Clinical characteristics, diagnostic criteria, and pathophysiology. *European Heart Journal*, *39*(22), 2032–2046.

Green, C. P., Porter, C. B., Bresnahan, D. R., & Spertus, J. A. (2000). Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. *Journal of the American College of Cardiology*, *35*(5), 1245–1255.

Grodstein, F., & Stampfer, M. (1995). The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Progress in Cardiovascular Diseases*, *38*(3), 199–210.

Haghi, D., Roehm, S., Hamm, K., Harder, N., Suselbeck, T., Borggrefe, M., & Papavassiliu, T. (2010). Takotsubo cardiomyopathy is not due to plaque rupture: An intravascular ultrasound study. *Clinical Cardiology*, *33*(5), 307–310.

Ionescu, C. N., Aguilar-Lopez, C. A., Sakr, A. E., Ghantous, A. E., & Donohue, T. J. (2010). Long-term Outcome of Tako-tsubo Cardiomyopathy. *Heart, Lung and Circulation*, *19*(10), 601–605.

Kendel, F., Spaderna, H., Sieverding, M., Dunkel, A., Lehmkuhl, E., Hetzer, R., & Regitz-Zagrosek, V. (2011). Eine deutsche Adaptation des ENRICHD Social Support Inventory (ESSI). *Diagnostica*, *57*(2), 99–106.

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders*, *74*(1), 5–13.

Khalighi, K., Farooq, M. U., Aung, T. T., & Oo, S. (2015). Takotsubo cardiomyopathy: A long term follow-up shows benefit with risk factor reduction. *Journal of Cardiovascular Development and Disease*, *2*(4), 273–281.

Khubchandani, J., Brey, R., Kotecki, J., Kleinfelder, J., & Anderson, J. (2016). The Psychometric Properties of PHQ-4 Depression and Anxiety Screening Scale Among College Students. *Archives of Psychiatric Nursing*, *30*(4), 457–462.

Khullar, M., Datta, B. N., Wahi, P. L., & Chakravarti, R. N. (1989). Catecholamine-induced experimental cardiomyopathy–A histopathological, histochemical and ultrastructural study. *Indian Heart Journal*, *41*(5), 307–313.

Klinceva, M., Widimsky, P., Pesl, L., Stasek, J., Tousek, F., Vambera, M., & Bílková, D. (2007). Prevalence of stress-induced myocardial stunning (Tako-Tsubo cardiomyopathy) among patients undergoing emergency coronary angiography for suspected acute myocardial infarction. *International Journal of Cardiology*, *120*(3), 411–413.

Kroenke, K., Spitzer, R. L., Williams, J. B., & Lowe, B. (2009). An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics*, *50*(6), 613–621.

Kurisu, S., Sato, H., Kawagoe, T., Ishihara, M., Shimatani, Y., Nishioka, K., & Nakamura, S. (2002). Tako-tsubo-like left ventricular dysfunction with ST-segment elevation: A novel cardiac syndrome mimicking acute myocardial infarction. *American Heart Journal*, *143*(3), 448–455.

Kurowski, V., Kaiser, A., von Hof, K., Killermann, D. P., Mayer, B., Hartmann, F., & Radke, P. W. (2007). Apical and midventricular transient left ventricular dysfunction syndrome (Tako-Tsubo Cardiomyopathy) frequency, mechanisms, and prognosis. *Chest*, *132*(3), 809–816.

Ladwig, K.-H., Baumert, J., Marten-Mittag, B., Lukaschek, K., Johar, H., Fang, X., … Peters, A. (2017). Room for depressed and exhausted mood as a risk predictor for all-cause and cardiovascular mortality beyond the contribution of the classical somatic risk factors in men. *Atherosclerosis*, *257*, 224–231.

Ladwig, K.-H., Lederbogen, F., Albus, C., Angermann, C., Borggrefe, M., Fischer, D., Fritzsche, K., Haass, M., Jordan, J. Jünger, J., Kindermann, I., Köllner, V., Kuhn, B., Scherer, M., Seyfarth, M.,

Völler, H., Waller, C. & Herrmann-Lingen, C. (2013). *Positionspapier zur Bedeutung psychosozialer Faktoren in der Kardiologie (Vol. 7)*.
Lazarus, R. S. (2006). *Stress and emotion: A new synthesis*. Springer Publishing Company. New York.
Lim, L. L., & Fisher, J. D. (1999). Use of the 12-item short-form (SF-12) health survey in an Australian heart and stroke population. *Quality of Life Research*, *8*(1–2), 1–8.
Lowe, B., Wahl, I., Rose, M., Spitzer, C., Glaesmer, H., Wingenfeld, K., … Brähler, E. (2010). A 4-item measure of depression and anxiety: Validation and standardization of the patient health questionnaire-4 (PHQ-4) in the general population. *Journal of Affective Disorders*, *122*(1–2), 86–95.
Madhavan, M., & Prasad, A. (2010). Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. *Herz*, *35*(4), 240–243.
Maron, B. J., Towbin, J. A., Thiene, G., Antzelevitch, C., Corrado, D., Arnett, D., & Young, J. B. (2006). Contemporary definitions and classification of the cardiomyopathies: An American heart association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation*, *113*(14), 1807–1816.
McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*(3), 873–904.
Michal, M., Schulz, A., Coldewey, M., Göbel, S., Prochaska, J., Ullmann, A., Beutel, M. E., Keller, K., Lamparter, H., Münzel, T., Reiner, I., Wild., P.S. (2015). *PHQ-2 and GAD-2 scores predict mortality in patients undergoing oral anticoagulation (Vol. 78)*.
Miller, G. E., Stetler, C. A., Carney, R. M., Freedland, K. E., & Banks, W. A. (2002). Clinical depression and inflammatory risk markers for coronary heart disease. *The American Journal of Cardiology*, *90*(12), 1279–1283.
Mostofsky, E., Maclure, M., Sherwood, J. B., Tofler, G. H., Muller, J. E., & Mittleman, M. A. (2012). Risk of acute myocardial infarction after the death of a significant person in one's life: The determinants of myocardial infarction onset study. *Circulation*, *125*(3), 491–496.
Mudd, J. O., Kapur, N. K., Champion, H. C., Schulman, S. P., & Wittstein, I. S. (2007). Patients with stress-induced (Takotsubo) cardiomyopathy have an increased prevalence of mood disorders and antidepressant use compared to patients with acute myocardial infarction. *Journal of Cardiac Failure*, *13*(6), S176.
Müller-Nordhorn, J., Roll, S., & Willich, S. N. (2004). Comparison of the short form (SF)-12 health status instrument with the SF-36 in patients with coronary heart disease. *Heart*, *90*(5), 523–527.
Naqvi, T. Z., Naqvi, S. S., & Merz, C. N. (2005). Gender differences in the link between depression and cardiovascular disease. *Psychosomatic Medicine*, *67*(Suppl 1), S15–18.
Nguyen, S. B., Cevik, C., Otahbachi, M., Kumar, A., Jenkins, L. A., & Nugent, K. (2009). Do comorbid psychiatric disorders contribute to the pathogenesis of tako-tsubo syndrome? A review of pathogenesis. *Congestive Heart Failure*, *15*(1), 31–34.
Nübling, M., Andersen, H. H., & Mühlbacher, A. (2006). Entwicklung eines Verfahrens zur Berechnung der körperlichen und psychischen Summenskalen auf Basis der SOEP-Version des SF 12 (Algorithmus) (No. 16). DIW Data Documentation.Berlin.
O'Leary, V. E., & Ickovics, J. R. (1995). Resilience and thriving in response to challenge: An opportunity for a paradigm shift in women's health. *Women's Health*, *1*(2), 121–142.
Parodi, G., Del Pace, S., Carrabba, N., Salvadori, C., Memisha, G., Simonetti, I., & Gensini, G. F. (2007). Incidence, clinical findings, and outcome of women with left ventricular apical ballooning syndrome. *The American Journal of Cardiology*, *99*(2), 182–185.
Penninx, B. W. J. H. (2017). Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neuroscience & Biobehavioral Reviews*, *74*, 277–286.
Petrowski, K., Paul, S., Albani, C., & Brähler, E. (2012). Factor structure and psychometric properties of the Trier Inventory for Chronic Stress (TICS) in a representative German sample. *BMC Medical Research Methodology*, *12*(1), 42.

Pettersen, K. I., Kvan, E., Rollag, A., Stavem, K., & Reikvam, A. (2008). Health-related quality of life after myocardial infarction is associated with level of left ventricular ejection fraction. *BMC Cardiovascular Disorders*, *8*, 28.

Pilgrim, T. M., & Wyss, T. R. (2008). Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. *International Journal of Cardiology*, *124*(3), 283–292.

Redfors, B., Vedad, R., Angeras, O., Ramunddal, T., Petursson, P., Haraldsson, I., … Omerovic, E. (2015). Mortality in takotsubo syndrome is similar to mortality in myocardial infarction - A report from the SWEDEHEART registry. *International Journal of Cardiology*, *185*, 282–289.

Resnick, B., & Parker, R. (2001). Simplified scoring and psychometrics of the revised 12-item short-form health survey. *Outcomes Management for Nursing Practice*, *5*(4), 161–166.

Roebuck, A., Furze, G., & Thompson, D. R. (2001). Health-related quality of life after myocardial infarction: An interview study. *Journal of Advanced Nursing*, *34*(6), 787–794.

Roest, A. M., Carney, R. M., Freedland, K. E., Martens, E. J., Denollet, J., & de Jonge, P. (2013). Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study. *Journal of Affective Disorders*, *149*(1–3), 335–341.

Rosengren, A., Hawken, S., Ôunpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., … Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): Case-control study. *The Lancet*, *364*(9438), 953–962.

Rosman, L., Dunsiger, S., & Salmoirago-Blotcher, E. (2017). Cumulative impact of stressful life events on the development of takotsubo cardiomyopathy. *Annals of Behavioral Medicine*, *51*(6), 925–930.

Salmoirago-Blotcher, E., Rosman, L., Wittstein, I. S., Dunsiger, S., Swales, H. H., Aurigemma, G. P., & Ockene, I. S. (2016). Psychiatric history, post-discharge distress, and personality characteristics among incident female cases of takotsubo cardiomyopathy: A case-control study. *Heart & Lung : the Journal of Critical Care*, *45*(6), 503–509.

Sato, H. (1990). Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. *Clinical Aspects of Myocardial Injury: from Ischemia to Heart Failure*, 56–64.

Scally, C., Rudd, A., Mezincescu, A., Wilson, H., Srivanasan, J., Horgan, G., & Dawson, D. K. (2018). Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy. *Circulation*, *137*(10), 1039–1048.

Schneider, B., Athanasiadis, A., Schwab, J., Pistner, W., Scheidt, W. V., Gottwald, U., & Sechtem, U. (2010). Klinische Versorgung von Patienten mit Tako-Tsubo-Kardiomyopathie. [Clinical spectrum of tako-tsubo cardiomyopathy in Germany]. *Deutsche medizinische Wochenschrift (1946)*, *135*(39), 1908–1913.

Schofer, N., Hamm, C., Katus, H. A., Kelm, M., & Blankenberg, S. (2014). Kommentar zur dritten allgemeinen Definition des Myokardinfarktes der gemeinschaftlichen ESC/ACCF/AHA/WHF Task Force. *Der Kardiologe*, *8*(1), 65–71.

Schulz, P., & Schlotz, W. (1999). Trierer Inventar zur Erfassung von chronischem Streß (TICS): Skalenkonstruktion, teststatistische Überprüfung und Validierung der Skala Arbeitsüberlastung. *Diagnostica*, *45*(1), 8–19.

Sharkey, S. W., Windenburg, D. C., Lesser, J. R., Maron, M. S., Hauser, R. G., Lesser, J. N., & Maron, B. J. (2010). Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *Journal of the American College of Cardiology*, *55*(4), 333–341.

Sieverding, M., Kendel, F., & Böhmer, S. (2004). Kann Coping belasten? Bewältigungsstrategien bei Mann und Frau. *Psychomed: Zeitschrift für Psychologie und Medizin*, *16*(1), 49–54.

Singh, K., Carson, K., Usmani, Z., Sawhney, G., Shah, R., & Horowitz, J. (2014). Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *International Journal of Cardiology*, *174*(3), 696–701.

Smeijers, L., Szabo, B. M., & Kop, W. J. (2016). Psychological distress and personality factors in takotsubo cardiomyopathy. *Netherlands Heart Journal : Monthly Journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*, *24*(9), 530–537.

Smeijers, L., Szabo, B. M., van Dammen, L., Wonnink, W., Jakobs, B. S., Bosch, J. A., & Kop, W. J. (2015). Emotional, neurohormonal, and hemodynamic responses to mental stress in Tako-Tsubo cardiomyopathy. *The American Journal of Cardiology*, *115*(11), 1580–1586.

Sobue, Y., Watanabe, E., Ichikawa, T., Koshikawa, M., Yamamoto, M., Harada, M., & Ozaki, Y. (2017). Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate. *International Journal of Cardiology*, *235*, 87–93.

Summers, M. R., Lennon, R. J., & Prasad, A. (2010). Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): Potential pre-disposing factors? *Journal of the American College of Cardiology*, *55*(7), 700–701.

Tamres, L. K., Janicki, D., & Helgeson, V. S. (2002). Sex differences in coping behavior: A meta-analytic review and an examination of relative coping. *Personality and Social Psychology Review*, *6*(1), 2–30.

Templin, C., Ghadri, J. R., Diekmann, J., Napp, L. C., Bataiosu, D. R., Jaguszewski, M., & Lüscher, T. F. (2015). Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *The New England Journal of Medicine*, *373*(10), 929–938.

Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., & White, H. D. (2018). Fourth universal definition of myocardial infarction (2018). *Journal of the American College of Cardiology*, *72*(18), 2231–2264.

Vahia, V. N. (2013). Diagnostic and statistical manual of mental disorders 5: A quick glance. *Indian Journal of Psychiatry*, *55*(3), 220–223.

Valbusa, A., Abbadessa, F., Giachero, C., Vischi, M., Zingarelli, A., Olivieri, R., & Visconti, L. O. (2008). Long-term follow-up of Tako-Tsubo-like syndrome: A retrospective study of 22 cases. *Journal of Cardiovascular Medicine*, *9*(8), 805–809.

Wagnild, G. M., & Young, H. M. (1993). Development and psychometric evaluation of the resilience scale. *Journal of Nursing Measurement*, *1*(2), 165–178.

Wallström, S., Ulin, K., Määttä, S., Omerovic, E., & Ekman, I. (2016). Impact of long-term stress in Takotsubo syndrome: Experience of patients. *European Journal of Cardiovascular Nursing*, *15*(7), 522–528.

Ware, J., Jr., Kosinski, M., & Keller, S. D. (1996). A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care*, *34*(3), 220–233.

Wedekind, H., Möller, K., & Scholz, K. H. (2006). Tako-Tsubo-Kardiomyopathie. *Herz Kardiovaskuläre Erkrankungen*, *31*(4), 339–346.

Wittstein, I. S. (2016). The sympathetic nervous system in the pathogenesis of takotsubo syndrome. *Heart Failure Clinics*, *12*(4), 485–498.

8 Literaturverzeichnis

Albus, C., Ladwig, K.-H., & Herrmann-Lingen, C. (2014). Psychokardiologie: praxisrelevante Erkenntnisse und Handlungsempfehlungen. *DMW-Deutsche Medizinische Wochenschrift, 139*(12), 596-601.

Amigo, I., Cuesta, V., Fernández, A., & González, A. (1993). The effect of verbal instructions on blood pressure measurement. *Journal of hypertension, 11*(3), 293-296.

Aslaksen, P. M., & Flaten, M. A. (2008). The roles of physiological and subjective stress in the effectiveness of a placebo on experimentally induced pain. *Psychosomatic medicine, 70*(7), 811-818.

Ben-Shlomo, Y., & Kuh, D. (2002). A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. In: Oxford University Press.

Benedetti, F. (2014). *Placebo effects*: Oxford University Press, USA.

Benedetti, F., & Amanzio, M. (2011). The placebo response: how words and rituals change the patient's brain. *Patient education and counseling, 84*(3), 413-419.

Benedetti, F., Maggi, G., Lopiano, L., Lanotte, M., Rainero, I., Vighetti, S., & Pollo, A. (2003). Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome. *Prevention & Treatment, 6*(1), 1a.

Burgdorf, C., Kurowski, V., Bonnemeier, H., Schunkert, H., & Radke, P. W. (2008). Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies. *European Journal of Heart Failure, 10*(10), 1015-1019.

Christensen, A. V., Juel, K., Ekholm, O., Thrysøe, L., Thorup, C. B., Borregaard, B., . . . Berg, S. K. (2020). Significantly increased risk of all-cause mortality among cardiac patients feeling lonely. *Heart, 106*(2), 140-146.

Colloca, L., Lopiano, L., Benedetti, F., & Lanotte, M. (2005). *The placebo response in conditions other than pain.* Paper presented at the Seminars in Pain Medicine.

Colloca, L., & Miller, F. G. (2011). Harnessing the placebo effect: the need for translational research. *Philosophical Transactions of the Royal Society B: Biological Sciences, 366*(1572), 1922-1930.

de la Fuente-Fernández, R., Phillips, A. G., Zamburlini, M., Sossi, V., Calne, D. B., Ruth, T. J., & Stoessl, A. J. (2002). Dopamine release in human ventral striatum and expectation of reward. *Behavioural brain research, 136*(2), 359-363.

Delmas, C., Lairez, O., Mulin, E., Delmas, T., Boudou, N., Dumonteil, N., . . . Galinier, M. (2012). Anxiodepressive disorders and chronic psychological stress are associated with Tako-Tsubo cardiomyopathy. *Circulation Journal*, CJ-12-0759.

Elesber, A. A., Prasad, A., Lennon, R. J., Wright, R. S., Lerman, A., & Rihal, C. S. (2007). Four-Year Recurrence Rate and Prognosis of the Apical Ballooning Syndrome. *Journal of the American College of Cardiology, 50*(5), 448-452. doi:https://doi.org/10.1016/j.jacc.2007.03.050

Enck, P., Bingel, U., Schedlowski, M., & Rief, W. (2013). The placebo response in medicine: minimize, maximize or personalize? *Nature reviews Drug discovery, 12*(3), 191-204.

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., . . . Kelley, J. M. (2018). Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychotherapy and Psychosomatics, 87*(4), 204-210. doi:10.1159/000490354

Everson-Rose, S. A., & Lewis, T. T. (2005). Psychosocial factors and cardiovascular diseases. *Annu. Rev. Public Health, 26*, 469-500.

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Placebo effects: biological, clinical and ethical advances. *Lancet, 375*(9715), 686.

Frisaldi, E., Piedimonte, A., & Benedetti, F. (2015). Placebo and Nocebo Effects: A Complex Interplay Between Psychological Factors and Neurochemical Networks. *American Journal of Clinical Hypnosis, 57*(3), 267-284. doi:10.1080/00029157.2014.976785

Ghadri, J. R., Kato, K., Cammann, V. L., Gili, S., Jurisic, S., Di Vece, D., . . . Szawan, K. A. (2018). Long-term prognosis of patients with Takotsubo syndrome. *Journal of the American College of Cardiology, 72*(8), 874-882.

Ghadri, J. R., Ruschitzka, F., Lüscher, T. F., & Templin, C. (2014). Takotsubo cardiomyopathy: still much more to learn. *Heart, 100*(22), 1804. doi:10.1136/heartjnl-2013-304691

Grünbaum, A. (1994). The placebo concept in medicine and psychiatry. *Philosophical psychopathology*, 285-324.

Hadamitzky, M., Sondermann, W., Benson, S., & Schedlowski, M. (2018). Placebo effects in the immune system. In *International review of neurobiology* (Vol. 138, pp. 39-59): Elsevier.

Hróbjartsson, A., & Gøtzsche, P. C. (2004). Placebo interventions for all clinical conditions. *Cochrane database of systematic reviews*(2).

Jütte, R. (2013). The early history of the placebo. *Complementary Therapies in Medicine, 21*(2), 94-97. doi:https://doi.org/10.1016/j.ctim.2012.06.002

Kaptchuk, T., & Miller, F. (2015). Placebo Effects in Medicine. *New England Journal of Medicine, 373*(1), 8-9. doi:10.1056/NEJMp1504023

Ladwig, K.-H., Lederbogen, F., Albus, C., Angermann, C., Borggrefe, M., Fischer, D., . . . Jünger, J. (2013). Positionspapier zur Bedeutung psychosozialer Faktoren in der Kardiologie. *Der Kardiologe, 7*(1), 7-27.

Meissner, K. (2011). The placebo effect and the autonomic nervous system: evidence for an intimate relationship. *Philosophical Transactions of the Royal Society B: Biological Sciences, 366*(1572), 1808-1817.

Meissner, K. (2014). Placebo responses on cardiovascular, gastrointestinal, and respiratory organ functions. In *Placebo* (pp. 183-203): Springer.

Meissner, K., Bingel, U., Colloca, L., Wager, T. D., Watson, A., & Flaten, M. A. (2011). The placebo effect: advances from different methodological approaches. *Journal of Neuroscience, 31*(45), 16117-16124.

Meissner, K., & Ziep, D. (2011). Organ-specificity of placebo effects on blood pressure. *Autonomic Neuroscience, 164*(1), 62-66. doi:https://doi.org/10.1016/j.autneu.2011.06.006

Mudd, J. O., Kapur, N. K., Champion, H. C., Schulman, S. P., & Wittstein, I. S. (2007). Patients with stress-induced (takotsubo) cardiomyopathy have an increased prevalence of mood disorders and antidepressant use compared to patients with acute myocardial infarction. *Journal of Cardiac Failure, 13*(6), S176.

Pedersen, S. S., Von Känel, R., Tully, P. J., & Denollet, J. (2017). Psychosocial perspectives in cardiovascular disease. *European journal of preventive cardiology, 24*(3_suppl), 108-115.

Pierce, J. B., Kershaw, K. N., Kiefe, C. I., Jacobs Jr, D. R., Sidney, S., Merkin, S. S., & Feinglass, J. (2020). Association of childhood psychosocial environment with 30-year cardiovascular disease incidence and mortality in middle age. *Journal of the American Heart Association, 9*(9), e015326.

Pilgrim, T. M., & Wyss, T. R. (2008). Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: a systematic review. *International journal of cardiology, 124*(3), 283-292.

Pollo, A., Vighetti, S., Rainero, I., & Benedetti, F. (2003). Placebo analgesia and the heart. *Pain, 102*(1-2), 125-133.

Redfors, B., Vedad, R., Angerås, O., Råmunddal, T., Petursson, P., Haraldsson, I., . . . Ioaness, D. (2015). Mortality in takotsubo syndrome is similar to mortality in myocardial infarction—a report from the SWEDEHEART registry. *International journal of cardiology, 185*, 282-289.

Sato, H. (1990). Tako-tsubo-like left ventricular dysfunction due to multivessel coronary spasm. *Clinical aspects of myocardial injury: from ischemia to heart failure*, 56-64.

Sharkey, S. W., Windenburg, D. C., Lesser, J. R., Maron, M. S., Hauser, R. G., Lesser, J. N., . . . Maron, B. J. (2010). Natural History and Expansive Clinical Profile of Stress (Tako-Tsubo) Cardiomyopathy. *Journal of the American College of Cardiology, 55*(4), 333-341. doi:https://doi.org/10.1016/j.jacc.2009.08.057

Summers, M. R., Lennon, R. J., & Prasad, A. (2010). Pre-Morbid Psychiatric and Cardiovascular Diseases in Apical Ballooning Syndrome (Tako-Tsubo/Stress-Induced Cardiomyopathy): Potential Pre-Disposing Factors? *Journal of the American College of Cardiology, 55*(7), 700-701. doi:https://doi.org/10.1016/j.jacc.2009.10.031

Templin, C., Ghadri, J. R., Diekmann, J., Napp, L. C., Bataiosu, D. R., Jaguszewski, M., . . . Lüscher, T. F. (2015). Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *New England Journal of Medicine, 373*(10), 929-938. doi:10.1056/NEJMoa1406761

Valbusa, A., Abbadessa, F., Giachero, C., Vischi, M., Zingarelli, A., Olivieri, R., & Visconti, L. O. (2008). Long-term follow-up of Tako-Tsubo-like syndrome: a retrospective study of 22 cases. *Journal of cardiovascular medicine, 9*(8), 805-809.

von Känel, R. (2016). Evidenzbasierte Psychokardiologie – oder was vom Typ-A-Verhalten übrigblieb. *Praxis, 105*(25), 1483-1491. doi:10.1024/1661-8157/a002548

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., . . . Cohen, J. D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science, 303*(5661), 1162-1167.

Wilhelm, M., Winkler, A., Rief, W., & Doering, B. K. (2016). Effect of placebo groups on blood pressure in hypertension: a meta-analysis of beta-blocker trials. *Journal of the American Society of Hypertension, 10*(12), 917-929. doi:https://doi.org/10.1016/j.jash.2016.10.009

Zimmermann-Viehoff, F., Meissner, K., Koch, J., Weber, C. S., Richter, S., & Deter, H.-C. (2013). Autonomic effects of suggestive placebo interventions to increase or decrease blood pressure: A randomized controlled trial in healthy subjects. *Journal of Psychosomatic Research, 75*(1), 32-35. doi:https://doi.org/10.1016/j.jpsychores.2013.03.011

Danksagung

Mein Dank gilt meiner Familie, insbesondere meinen Eltern, ihnen widme ich diese Arbeit.

Darüber hinaus möchte ich mich bei Prof. Dr. med. habil. Karin Meißner für die inhaltliche, technische und emotionale Unterstützung bedanken, die notwendig war, diese Dissertation fertig zu stellen.

Nicht fehlen darf an dieser Stelle PD Dr. med. Joram Ronel, ich bin ihm sehr dankbar für sein Vertrauen in mich und meine Arbeit.

Zudem gilt mein Dank Dr. med. Simon Schneider, Dr. med. Daniel Sinnecker, Prof. Dr. med. habil. Georg Schmidt und Dipl. Ing. Alexander Müller aus dem Klinikum rechts der Isar, TU München und Dr. med. Siegmund Braun und Prof. Dr. med. Stefan Holdenrieder aus dem Deutschen Herzzentrum, TU München, ohne deren Hilfe, die Umsetzung der Studien nicht möglich gewesen wäre. Ich möchte hier ausdrücklich die beiden Teams der Kardiologischen Ambulanz des Klinikum rechts der Isar und des Labors im Deutschen Herzzentrum nennen, die mir immer hilfreich zur Seite gestanden sind. Für ihre Unterstützung möchte ich mich zudem bei Dr. med. Hansjörg Ebell und Prof. Dr. med. Karl-Heinz Ladwig bedanken.