Aus der Herzchirurgischen Klinik und Poliklinik der
Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. med. Christian Hagl

Arrhythmias after Cardiac Surgery

Kumulative Habilitationsschrift
zum Erlang der Venia Legendi
für das Fach Herzchirurgie
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Dr. med. Florian Ernst Martin Herrmann

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1. Publications Summarized within this Work

1. Wellmann P*, Herrmann FE*, Hagl C, Juchem G. A Single Center Study of 1,179 Heart Transplant Patients-Factors Affecting Pacemaker Implantation. Pacing and clinical electrophysiology : PACE Mar 2017;40:247-254. *Contributed equally

2. Herrmann FEM, Wellmann P, Sadoni S, Schramm R, Hagl C, Juchem G. Sinus node dysfunction after heart transplantation-An analysis of risk factors and atrial pacing burden. Clinical transplantation Mar 2018;32:e13202.

3. Herrmann FEM, Wellmann P, Hagl C, Juchem G. Pediatric heart transplantation-What are the risk factors for pacemaker implantation and how much pacing is required? Pacing and clinical electrophysiology : PACE Mar 2018;41:267-276.

4. Herrmann FEM, Graf H, Wellmann P, Sadoni S, Hagl C, Juchem G. Etiology of tricuspid valve disease is a predictor of bradyarrhythmia after tricuspid valve surgery. J Cardiovasc Electrophysiol. 2019 Jul;30(7):1108-1116.

5. Herrmann FEM, Graf H, Wellmann P, Sadoni S, Hagl C, Juchem G. Atrioventricular Block after Tricuspid Valve Surgery. Int Heart J. 2021 Jan 30;62(1):57-64.

6. Herrmann FEM, Schleith AS, Graf H, Sadoni S, Hagl C, Bagaev E, Juchem G. Tricuspid valve annuloplasty and mitral valve replacement are associated with bradyarrhythmia after mitral valve surgery. J Cardiovasc Electrophysiol. 2021 Apr;32(4):1103-1110.

7. Herrmann FEM, Ehrenfeld F, Wellmann P, Hagl C, Sadoni S, Juchem G. Thrombocytopenia and end stage renal disease are key predictors of survival in patients with cardiac implantable electronic device infections. J Cardiovasc Electrophysiol. 2020 Jan;31(1):70-79.

8. Charitos EI, Herrmann FEM, Ziegler PD. Atrial fibrillation recurrence and spontaneous conversion to sinus rhythm after cardiac surgery: Insights from 426 patients with continuous rhythm monitoring. J Cardiovasc Electrophysiol. 2021 Aug;32(8):2171-2178.

2. Background and Aims

The heart would not be without its internal rhythm. It is the cardiac conduction tissue which stimulates the myocardial tissue to contract and without this tissue dedicated to keeping the heart in beat the organ would not function. “Arrhythmia” comprises all forms of irregularity in the cardiac rhythm. While arrhythmia may present individually from further cardiac disorders patients who have undergone cardiac surgery have a comparatively high burden of arrhythmia (1-3). Since the dawn of cardiac surgery arrhythmia has been and will continue to remain intertwined with this surgical specialty.

Any manipulation of the heart may lead to an aggravation which can result in arrhythmia. Suture lines, tissue removal, patch implantation, prosthesis implantation and ablation may all have an effect on cardiac conduction and may result in changes in the rhythm in the form of bradyarrhythmia and tachyarrhythmia. Furthermore the mere manipulation of the heart in the form of open chest cardiac surgery is associated with tachyarrhythmia.

Within this habilitation endeavor the development of arrhythmia after cardiac surgery was investigated in several individual projects (see Figure 1). To start with the development of several forms of bradyarrhythmia after heart transplantation was studied. Here the incidence of sinus node dysfunction and atrioventricular block were elucidated. Risk factors for pacemaker requirement after surgery as well as for the development of sinus node dysfunction were identified. In the next step the development of bradyarrhythmia after tricuspid and mitral valve surgery were investigated. Here also the incidence and predictors of bradyarrhythmia were examined. As atrioventricular block constituted the most frequent bradyarrhythmia after tricuspid valve surgery its development after tricuspid valve surgery was examined in more detail in the form of an individual sub project.

After having concentrated on bradyarrhythmias for the main portion of this scientific research the next two projects involved the analysis of complications of device-based bradyarrhythmia therapy and an investigation of atrial fibrillation after cardiac surgery. The aim of all individual projects within this habilitation endeavor was to provide data which will inform cardiac surgeons and further clinicians treating patients having undergone cardiac surgery regarding these very important side effects of surgery. It was our hope in performing this research that a stronger understanding of postoperative arrhythmia may lead to an improvement of patient care after cardiac surgery.

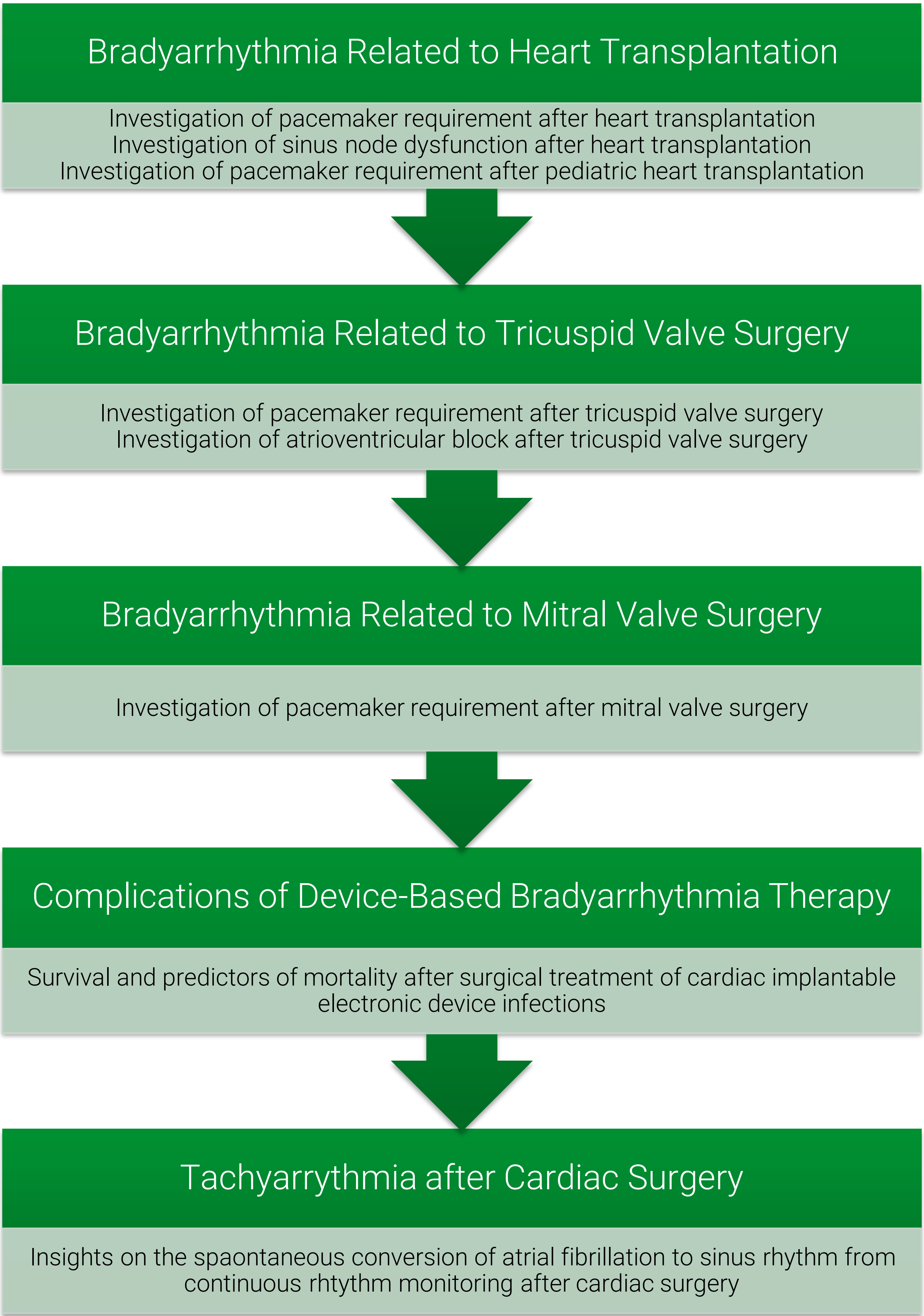


Figure 1 Flow chart of individual projects encompassing this habilitation endeavor. Below each project further sub-projects are listed.

3. Bradyarrhythmias Related to Heart Transplantation

Introduction

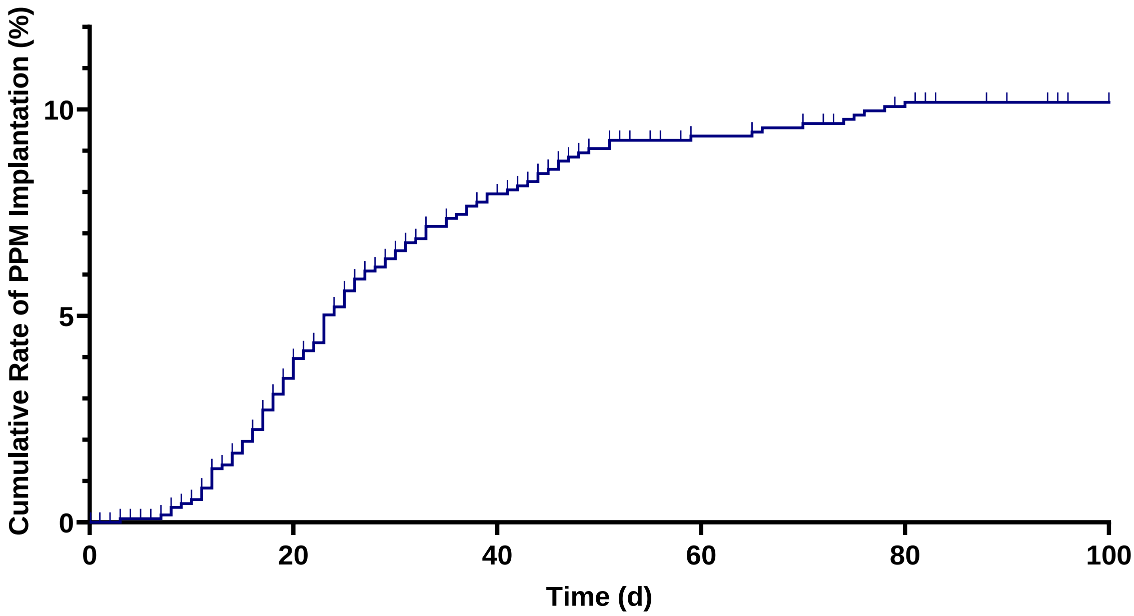
Heart transplantation remains the only curative therapy for terminal heart failure. Eligibility and perseverance during extended waiting time (4) are key hurdles during this treatment. However, the burden of disease does not end with successful transplantation as there are a host of secondary afflictions affecting the transplanted patient (5). One of these afflictions is arrhythmia. While tachyarrhythmias such as atrial fibrillation and atrial flutter may be temporal occurrences and can generally be treated conservatively (6), bradyarrhythmic complications may require more permanent treatment i.e. implantation of a permanent pacemaker.

It is especially in the transplant patient that the implantation of devices should be carefully evaluated. Immunosuppressive medication puts the transplant patient at an increased risk of infections (7, 8). The surgical implantation of a permanent pacemaker is associated with a risk of infection (9) which can have dire consequences for patients (10, 11) due to the transvenous path of endocardial pacemaker leads. It is for these reasons that the issue of pacemaker requirement after heart transplantation plays a critical role for the heart transplant clinician.

The first heart transplant documented in our departmental database was performed 1981. With an active logging of 1 179 patients in a period spanning from 1981 until 2016 we thus have access to a large dataset with the potential of unveiling important knowledge in this field. It is this massive data content that we exploited in our attempt to better understand the issue of bradyarrhythmia after heart transplantation. While several small series regarding this topic were available prior to our investigation, no series summed up data from such a large cohort. It was our aim to provide a better understanding of indications, risk factors and pacing burden after pacemaker implantation post heart transplantation. Due to the clear differences between pediatric and adult heart transplantation (mainly affecting patient and donor size, life expectancy, etc.) we performed a subgroup analysis investigating bradyarrhythmias in the pediatric cohort separately.

Pacemaker Implantation Rates after Heart Transplantation

In our analysis of 1 179 patients who had received a heart transplant, 240 (20.4%) recipients were female and the mean recipient age was 45.5 years. Within this cohort 135 patients (11.5%) required pacemaker implantation for bradyarrhythmia. 116 (87.2%) permanent pacemakers (PPM) were implanted for sinus node dysfunction (SND) while 17 (12.8%) were implanted for atrioventricular block (AVB). The cumulative rates of permanent pacemaker implantation over time are depicted in Figure 2 below.



No. at Risk					
1179	1009	932	893	873	862
Cumulative Events					
0	42	83	97	105	105

Figure 2 Cumulative rate of permanent pacemaker implantation within the first 100 days after heart transplantation. PPM: permanent pacemaker; the Kaplan-Meier method was used for the generation of this graph.

Predictors of Pacemaker Implantation after Heart Transplantation

Individual procedural data differed between the patients who postoperatively required pacemakers and those who did not. Those requiring pacemakers were found to have had a significantly longer operative time (340 min. vs. 313 min.; P = 0.030) and have undergone a biatrial anastomosis (compared to a bicaval anastomosis) more frequently (95.6% vs. 89.9%; P = 0.036). Schematics displaying the operative differences between the biatrial and bicaval techniques can be found in Figure 3 on the following page. Ischemia time, cardiopulmonary bypass time and aortic cross clamp time were not found to be significantly different in patients later requiring a pacemaker compared to those not requiring a pacemaker (see Figure 4).

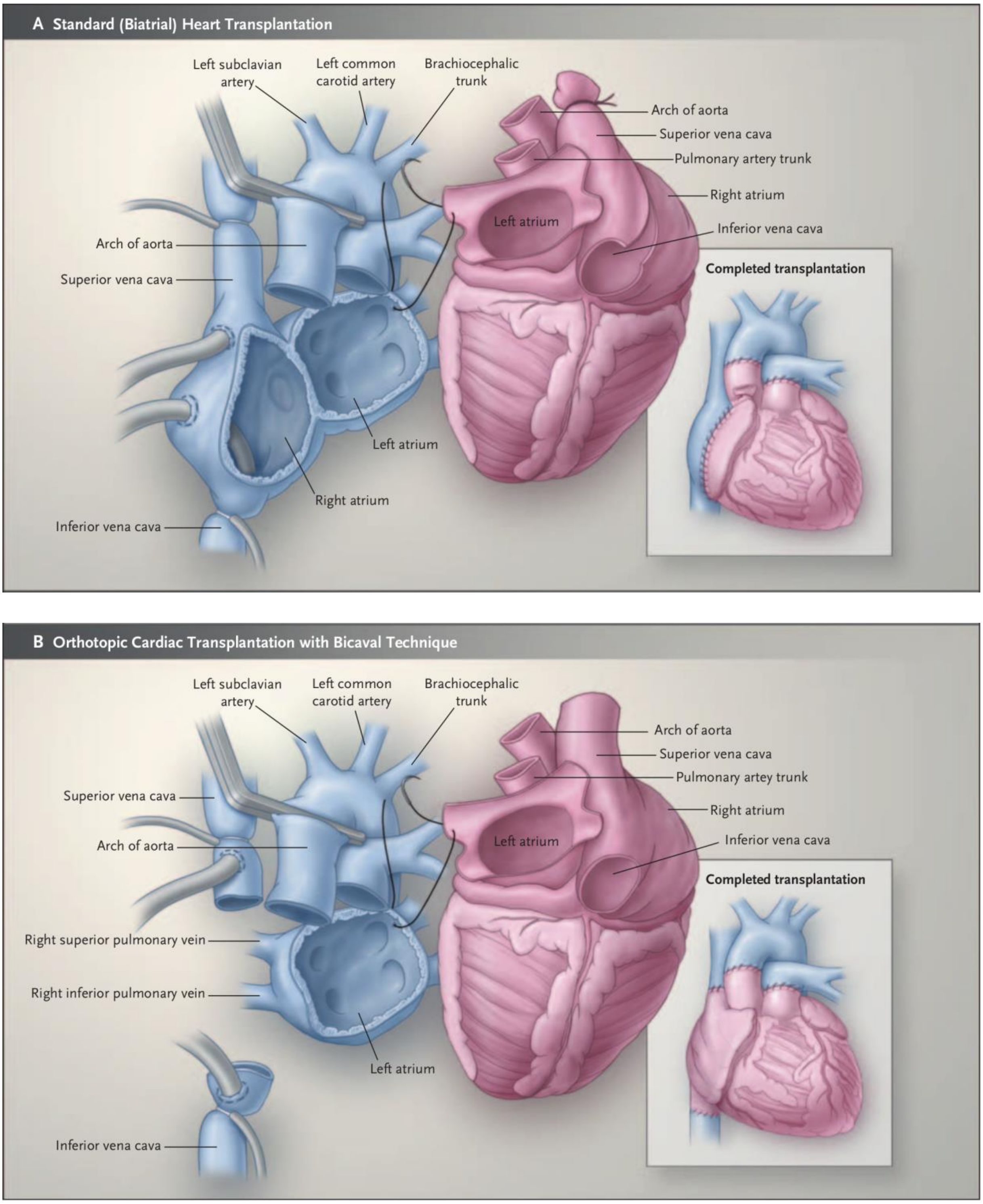


Figure 3 Illustration of the two most frequently applied operative techniques for orthotopic heart transplantation. (A)the standard biatrial transplantation technique first described by Lower and Shumway (12); (B) the bicaval technique first described by Banner and Yacoub (13).

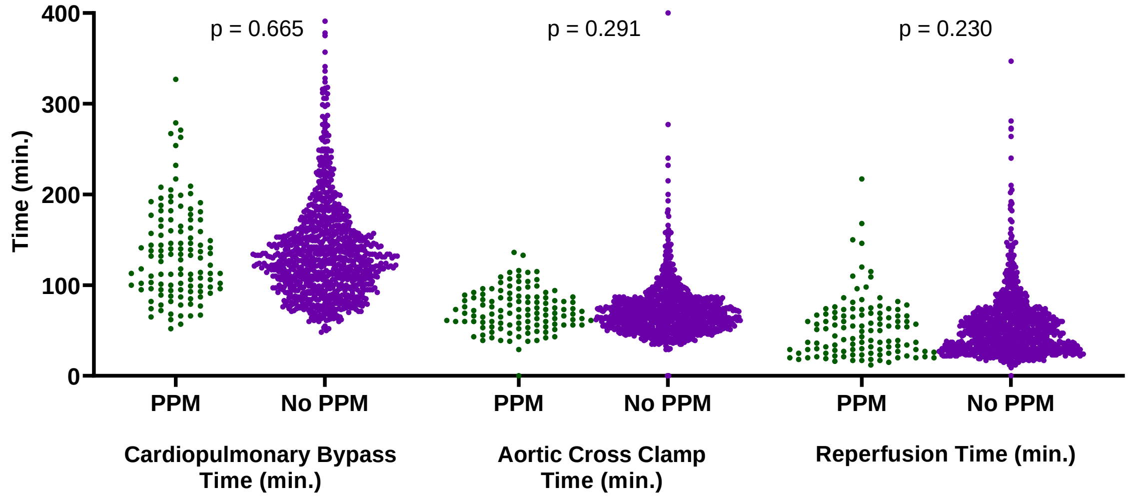


Figure 4 Scatter plots of the cardiopulmonary bypass, aortic cross clamp and reperfusion time during heart transplantation with a comparison of patients who required permanent pacemaker implantation after surgery and those who didn't. PPM: patients who required permanent pacemakers after surgery; No PPM: patients who didn't require permanent pacemakers after surgery.

Differences in Heart Transplant Patients with SND vs. AVB

Patients who required pacemakers for SND were compared with patients requiring a pacemaker for AVB (Table 1). This comparison showed that the donor age in the AVB group was significantly higher (42.63 vs. 34.33 years; P = 0.031), the cardiopulmonary bypass time was significantly longer (169.67 vs. 132.16 min.; P = 0.019) and the aortic cross clamp time was significantly longer (84.00 vs. 70.69 min.; P = 0.033). As displayed in Figure 5 the median time between heart transplant and pacemaker implantation was significantly longer for patients with AVB than for patients with SND (805 days vs. 26.5 days; P = 0.042).

Patient's Requiring Permanent Pacemaker Implantation after Heart Transplantation

	All PPM Patients (=135)	SE	Sinus Node Dysfunction (=116)	SE	Atrio-ventricular Block (=17)	SE	P value
Percentage of patients	135 (100%)		116 (87.2%)		17 (12.8%)		
Female recipients	27 (20.3%)		22 (19.0%)		5 (29.4%)		0.338
Recipient age (y)	46.71	1.36	46.49	1.48	48.21	3.28	0.835
Donor age (y)	35.44	1.31	34.33	1.39	42.63	3.42	**0.031**
Ischemia time (min.)	220.96	6.44	220.79	7.02	222.14	15.88	0.945
Operative time (min.)	340.04	14.58	321.45	13.42	431.54	49.80	**0.019**
Cardiopulmonary Bypass Time (min.)	136.97	4.87	132.16	5.03	169.67	14.38	**0.014**
Aortic Cross Clamp Time (min.)	72.39	2.09	70.69	2.24	84.00	5.04	**0.033**
Reperfusion Time (min.)	52.76	3.13	50.74	3.22	67.29	10.67	0.154
Median time to pacemaker implantation. (d)	29.00		26.50		805.00		**0.042**
Pacemaker implantation within 3 months of transplant	104 (78.8%)		97 (83.6%)		7 (43.8%)		**0.001**

Table 1 Comparison of patients requiring a pacemaker for sinus node dysfunction versus atrioventricular block after heart transplantation. PPM: patients requiring a permanent pacemaker after heart transplantation; SE: standard error of the mean; Sinus node dysfunction: patients requiring a permanent pacemaker for sinus node dysfunction after heart transplantation; Atrioventricular block: patients requiring a permanent pacemaker for atrioventricular block after heart transplantation.

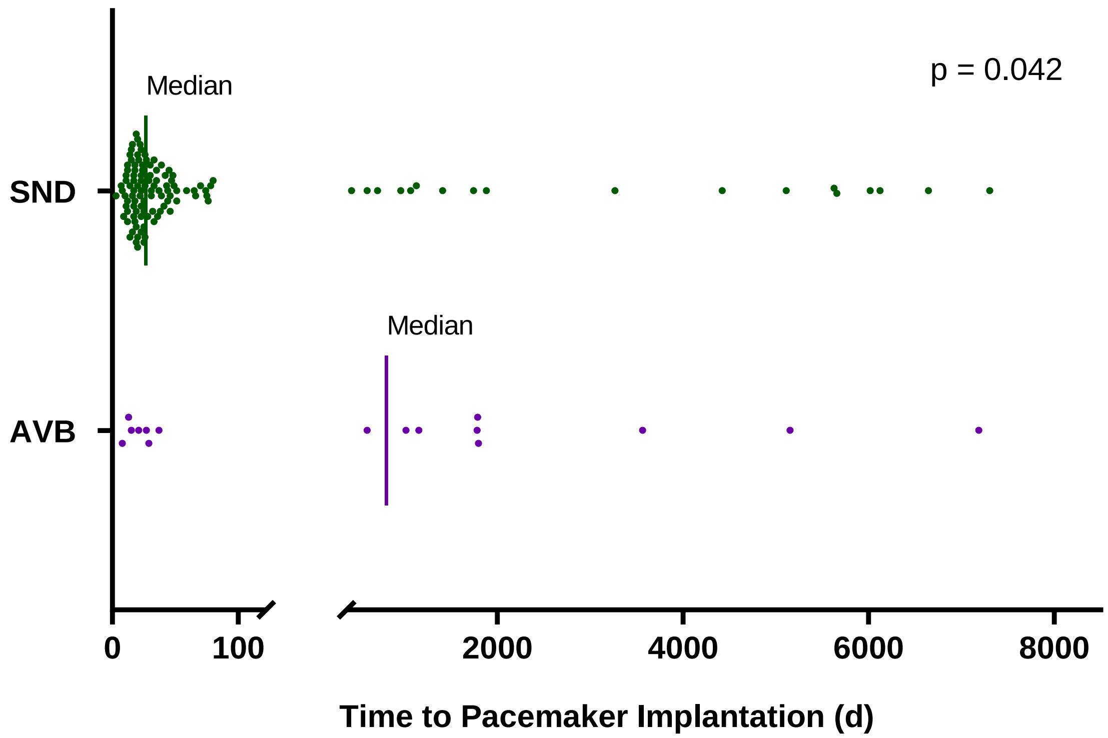


Figure 5 Time point of pacemaker implantation after heart transplantation depending on indication. Note that the scale of the two separate x axis segments differs. SND: patients requiring a pacemaker for sinus node dysfunction; AVB: patients requiring a pacemaker for atrioventricular block. Vertical lines indicate the respective medians.

Atrial Pacing Burden in Patients with Sinus Node Dysfunction after Heart Transplantation

Patients with sinus node dysfunction constitute the largest group of patients requiring pacemakers after heart transplantation. In an attempt to quantify the pacing burden[A] in these patients, device interrogation data from all patients with single lead atrial pacemakers was collected. This analysis showed that early after pacemaker implantation the mean pacing burden was highest (see Figure 6). Within the first 6 years after surgery, the pacing burden reduced but never went under a mean of 60 % pacing burden.

[A] Pacing burden describes the percentage of time that a pacemaker is actively pacing the heart.

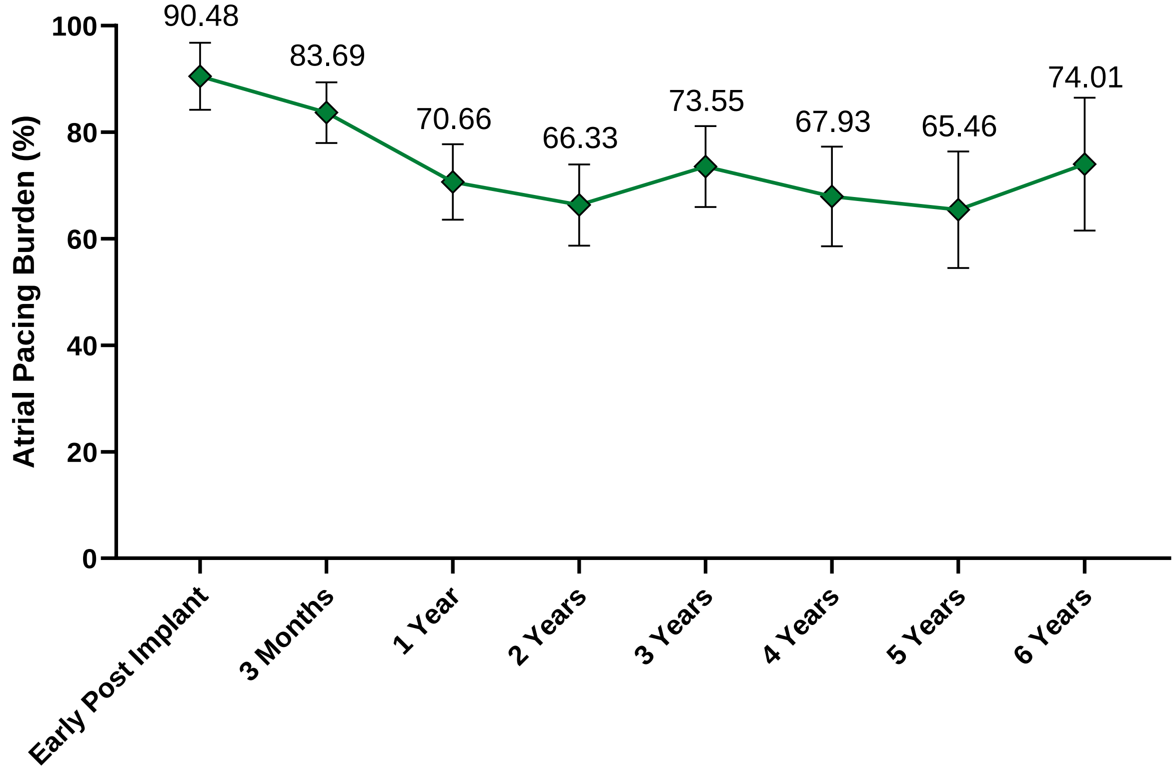


Figure 6 Mean atrial pacing burden in patients who received a single lead atrial pacemaker for sinus node dysfunction after heart transplantation. Pacing burden was defined as percentage of time paced. Error bars: standard error of the mean.

Figure adapted from Herrmann et al. Sinus node dysfunction after heart transplantation-an analysis of risk factors and atrial pacing burden. Clinical transplantation 2018;32(3):e13202 with permission of John Wiley & Sons A/S, Copyright 2018. (16)

Survival in Patients with Pacemakers Implanted after Heart Transplantation

Including all patients who had undergone heart transplantation in our institution (beginning 1981) we calculated a survival of 71 % at 5 years and 59 % at 10 years. It must be noted that the timeframe covered by this study includes the early years of heart transplantation, when transplant care with all its nuances was being developed. Kaplan-Meier analysis of the survival in patients who had undergone pacemaker implantation and those who had not undergone pacemaker implantation after heart transplantation showed that survival does not differ ($P = 0.197$ in the log rank test). Survival analysis was performed using the landmark methodology by which the effect of early mortality after surgery (which is most likely not affected by pacemaker implantation) is factored out.

Pacemaker Implantation Rates and Indications after Pediatric Heart Transplantation

In our analysis of 139 patients who had received a heart transplant at an age under 18 years, 61 (43.9%) recipients were female and the median recipient age was 9.51 years. In 59 cases (46.1%)

the donor was female. 17 patients (12.2%) underwent pacemaker implantation after heart transplantation. Of these 13 (76.5%) required a pacemaker for sinus node dysfunction and four 23.5%) for atrioventricular block.

Risk Factors for Pacemaker Implantation after Pediatric Heart Transplantation

In univariable analysis a significant difference was detected in the donor age, donor height and donor weight in patients who later required a pacemaker compared to those who did not. In patients requiring a pacemaker after surgery the median donor age was 13 years greater than in those who did not require a pacemaker (see Figure 7). Comparing the age gap between donor and recipient (donor age – recipient age) showed that the median difference in patients not requiring a pacemaker was 0.988 while the median difference in patients requiring a pacemaker was 10.125 (P = 0.010). Concordantly the height and weight of the donors to patients later requiring a pacemaker was greater than that of donors to patients not requiring a pacemaker (160 cm vs. 141 cm; P = 0.015 and 61 kg vs. 48 kg; P = 0.032). In multivariable analysis donor age, height and weight were analyzed – here only donor age was found to be a significant risk factor (P = 0.035). Anastomotic technique (biatrial or bicaval), ischemia time and operative time were not found to be predictors of pacemaker requirement after pediatric heart transplantation.

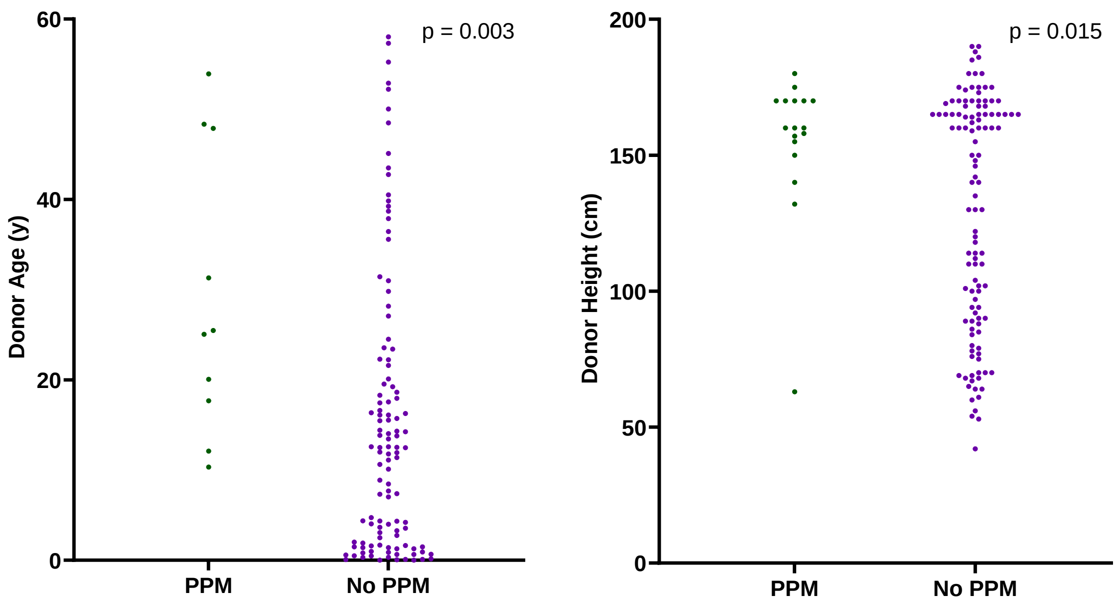


Figure 7 Scatter plots depicting donor age and donor height in pediatric patients requiring permanent pacemaker implantation after heart transplantation and those not. PPM: patients requiring a pacemaker after heart transplantation; No PPM: patients not requiring a pacemaker after heart transplantation. Statistical values are the result of univariable testing.

Survival in Pediatric Patients with Pacemakers Implanted after Heart Transplantation

In this pediatric cohort, we calculated a mean survival of 17.28 years (confidence interval: 15.37–19.18). The survival at 10 years was 70.8%. Kaplan-Meier analysis did not show a significant difference in the survival of patients who had received a pacemaker after surgery compared to those who did not receive a pacemaker (P = 0.672 in the log rank test).

Conclusion

In the described project spanning several individual analyses of patients who underwent heart transplantation in our institution, we were able to expand our understanding within this field. We determined that in adults as well as in pediatric patients over 10 % develop bradyarrhythmia leading to pacemaker implantation. In adults as well as in children most pacemakers are required for postoperative sinus node dysfunction. Predictors of bradyarrhythmia differ in the complete heart transplant population compared to the pediatric population. While in the complete population the anastomotic technique and operative time significantly differ in the pacemaker group as compared to the no pacemaker group, in the pediatric population donor factors e.g. donor age seem to play a key role. In patients with sinus node dysfunction, which constitutes the largest population of heart transplant patients requiring pacemaker implantation, device interrogation data shows that, years after surgery pacing burden remains high. This suggests that the rhythm disorders are not a temporary occurrence but rather a long-term issue and that the patients will require long-term care in a pacemaker unit.

4. Bradyarrhythmias Related to Tricuspid Valve Surgery

Introduction

The tricuspid valve has an intimate relationship to cardiac conduction tissue (see Figure 8 and Figure 9) and conduction tissue is at high risk of damage during surgery of this valve (17-19). The atrioventricular node and the penetrating bundle of His regulate the conduction between the atria and ventricles and both lie in close proximity of the tricuspid valve (20). Moreover the necessity of bicaval cannulation, the application of snares in the proximity of right atrial tissue as well as the incision and suturing of right atrial tissue all result in a risk for arrhythmia after tricuspid valve surgery.

The consequence of bradycardic rhythm disturbances in patients post tricuspid valve surgery are severe. The implantation of an endocardial right ventricular pacing lead in a patient who has undergone tricuspid valve repair has been shown to have a negative effect on the long-term durability of repair procedures (21, 22). In patients who have undergone mechanical tricuspid valve prosthesis, implantation endocardial right ventricular lead implantation is contraindicated and in patients who have undergone biological prosthesis implantation endocardial lead implantation is possible (23) but may put long term valve function at risk.

It is due to the consequences that pacemaker therapy have on the tricuspid valve patient that it is important to fully understand pacemaker requirement after tricuspid valve surgery. It is critical to be able to identify patients at risk as this may lead the surgeon to make use of epicardial leads (19) which subsequently spare the tricuspid valve or tricuspid prosthesis of the strain of an endocardial lead. Limited literature is available on rhythm disturbances after tricuspid valve surgery. It was our aim to fill the void and to provide detailed data from a very large patient cohort (18, 19).

We investigated all patients who underwent any surgical procedure of the tricuspid valve in the Department of Cardiac Surgery of the Ludwig Maximilian University, Munich (LMU) from 2004 until 2017. All patients who had undergone pacemaker implantation prior to surgery were excluded. Subsequently 505 patients were included in our analysis. In a first step, we investigated all patients who received pacemakers for any bradyarrhythmia within the first 50 days after surgery. In a second step, we investigated all patients who received pacemakers due to atrioventricular block, which constituted the most frequent indication for pacemaker implantation. Here we were especially interested in the ventricular pacing burden after pacemaker implantation.

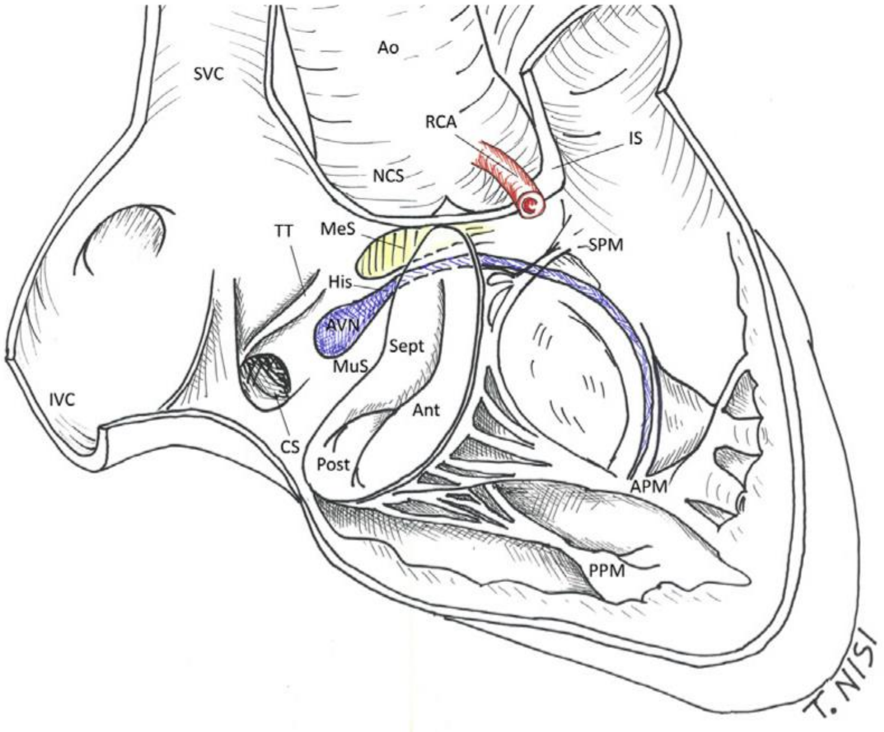


Figure 8 Schematic representation of the right atrium, tricuspid valve and right ventricle. Ant, anterior leaflet; Ao, aorta; APM, anterior papillary muscles; AVN, AV node; CS, coronary sinus ostium; His, bundle of His; IS, infundibular septum; IVC, inferior vena cava; MeS, septum membranosum; MuS, muscular portion of the AV septum; NCS, noncoronary sinus of the aorta; Post, posterior leaflet; PPM, posterior papillary muscle; Sept, septal leaflet; SPM, septal papillary muscle; SVC, superior vena cava; TT, tendon of Todaro.

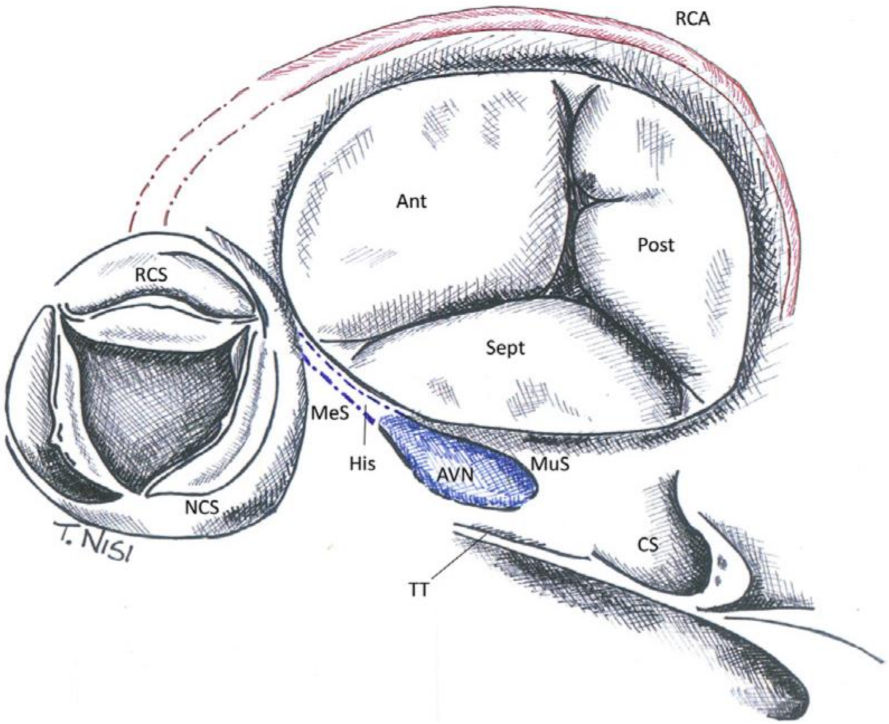
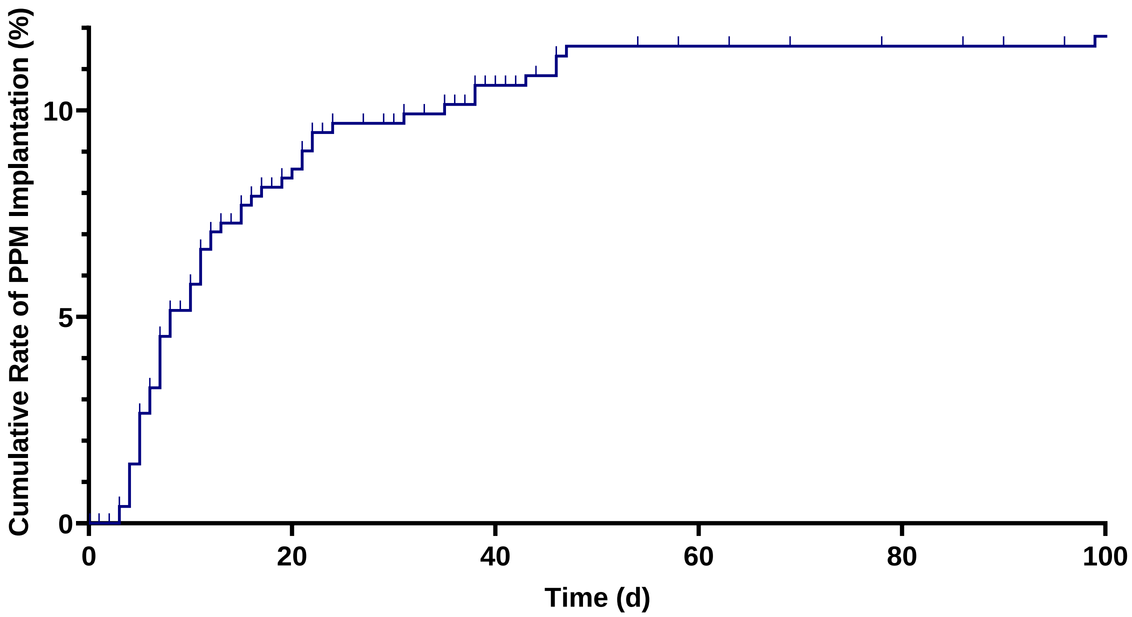


Figure 9 Schematic representation of the surgical view of the tricuspid valve from the right atrium. Ant, anterior leaflet; AVN, AV node; CS, coronary sinus ostium; His, bundle of His; MeS, septum membranosum; MuS, muscular portion of the AV septum; NCS, noncoronary sinus of the aorta; Post, posterior leaflet; RCS, right coronary sinus of the aorta; Sept, septal leaflet; TT, tendon of Todaro.

Pacemaker Implantation Rates

Our complete cohort had a maximum follow-up time of 14.2 years and a median follow-up time of 4.0 years (95 % confidence interval (CI): 3.6 - 4.4 years). Throughout follow-up 77 of the 505 patients (15.2%) required pacemaker implantation for bradyarrhythmia after surgery.

Time specific pacemaker implantation rates were calculated using the Kaplan-Meier method. This methodology takes into account when patients have deceased and are no longer available for the statistic regarding risk for pacemaker implantation. The following are the pacemaker implantation rates at different points in time after surgery: 10% (CI: 7.2 - 12.6) at 1 month, 13% (CI: 9.7 - 15.8) at 1 year, 14.5% (CI: 11.1 - 17.7) at 2 years, 17.5% (CI: 13.5 - 21.3) at 4 years and 25.5% (CI: 16.7 - 33.4) at 10 years. The cumulative rates of permanent pacemaker implantation over time are depicted in Figure 10 below.



No. at Risk

505	417	383	372	368	363

Cumulative Events

0	41	50	54	54	55

Figure 10 Cumulative rate of permanent pacemaker implantation within the first 100 days after tricuspid valve surgery. PPM: permanent pacemaker; the Kaplan-Meier method was used for the generation of this graph.

Figure adapted from Herrmann et al. Etiology of tricuspid valve disease is a predictor of bradyarrhythmia after tricuspid valve surgery. Journal of cardiovascular electrophysiology 2019;30(7):1108-1116 with permission from Wiley Periodicals, Inc. Copyright 2019. (24)

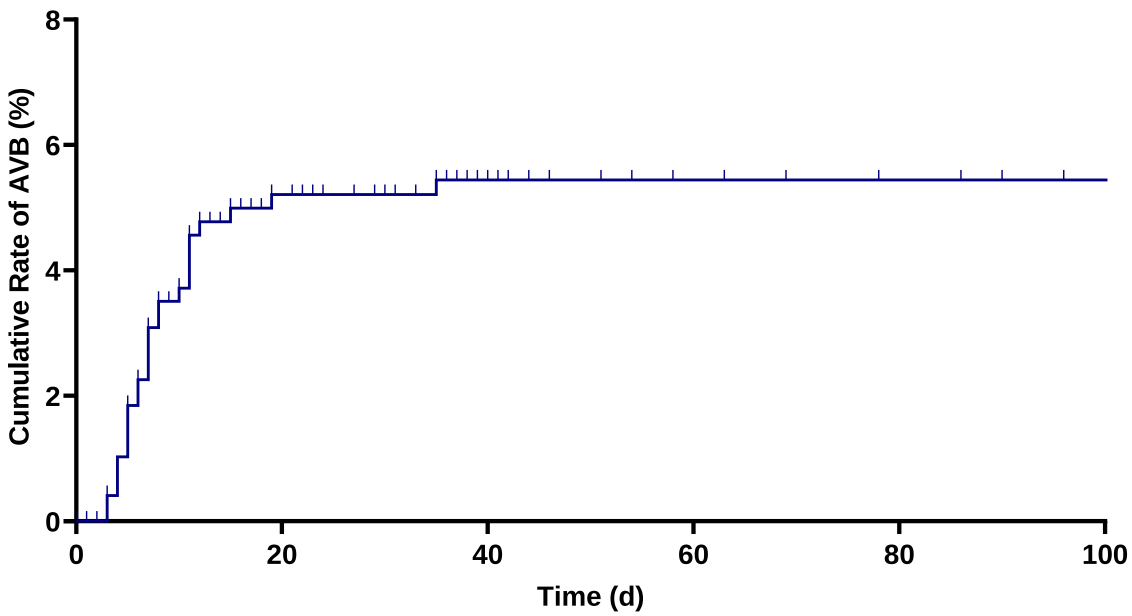
Indications for Pacemaker Implantation

Of the 77 patients who had undergone pacemaker implantation throughout follow-up 33 (42.9%) suffered from atrioventricular block (AVB), 26 (33.8%) suffered from sinus node dysfunction and 18 (23.4%) from atrial fibrillation (AF) with a slow ventricular rate.

Of the 54 patients who had undergone pacemaker implantation within 50 days of surgery 26 (48.1%) suffered from atrioventricular block (AVB), 16 (29.6%) suffered from sinus node dysfunction and 12 (22.2%) from atrial fibrillation with a slow ventricular rate.

Rate of Pacemaker Implantation for Atrioventricular Block

As mentioned above throughout follow-up in the complete cohort 33 of 505 patients (6.5%) required pacemaker implantation for atrioventricular block. The following are the pacemaker implantation rates for AVB at different points in time: 5.2% (CI: 3.2 - 7.2) at 1 month, 5.8% (CI: 3.6 - 7.8) at 1 year, 6.9% (CI: 4.4 - 9.3) at 5 years and 8.1% (CI: 4.6 - 11.5) at 10 years. The cumulative rates of pacemaker implantation for AVB over time are depicted in Figure 11.



No. at Risk					
505	430	406	397	393	389
Cumulative Events					
0	25	26	26	26	26

Figure 11 Cumulative rate of atrioventricular block within the first 100 days after tricuspid valve surgery. AVB: atrioventricular block. Atrioventricular block was defined as atrioventricular block leading to permanent pacemaker implantation. The Kaplan-Meier method was used for the generation of this graph.

Figure adapted from Herrmann et al. Atrioventricular block after tricuspid valve surgery. Int Heart J 2021;62(1):57-64 with permission of International Heart Journal. Copyright International Heart Journal 2021. (25)

Predictors of Pacemaker Implantation

In the analysis of patients requiring a pacemaker for any bradyarrhythmia after tricuspid valve surgery multivariable analysis identified active endocarditis (odds ratio 3.17; CI: 1.32 - 7.65; P = 0.010) and an "inadequate pacemaker dependent rhythm" [B] at intensive care unit (ICU) admission (odds ratio 5.92; CI: 2.82 – 12.44; P = 0.001) as significant predictors of pacemaker implantation after surgery. Tricuspid valve replacement was associated with a higher rate of AVB in univariable analysis (P = 0.002). Furthermore a higher rate of tricuspid valve replacement was detected in patients with tricuspid valve endocarditis (21 of 38 cases [55.3%]; P = 0.001). This possible confounding association between the surgical procedure performed on the tricuspid valve and active endocarditis must be kept in mind when interpreting the results.

Predictors of Pacemaker Implantation for Atrioventricular Block

Of 37 patients presenting with third degree atrioventricular block at admission to the ICU directly postoperatively only 14 patients (38%) required pacemaker implantation postoperatively. High grade AVB at ICU admission was identified as a predictor of pacemaker implantation for AVB (odds ratio: 9.7; CI: 3.8 – 24.5; P < 0.001) in multivariable logistic regression analysis. Tricuspid valve endocarditis was also identified as a predictor of pacemaker implantation for AVB (odds ratio: 12.4; CI: 3.3 – 46.3, P < 0.001) in multivariable analysis.

Pacing Burden in Patients with Atrioventricular Block

Making use of device interrogation reports we were able to analyze the pacing burdens and intrinsic heart rates in patients who had undergone pacemaker implantation for atrioventricular block after tricuspid valve surgery. The mean ventricular pacing burden within the complete patient group throughout the complete follow-up period was 79%. The mean intrinsic heart rate was 44/min. Analysis of data from the first 5 years after pacemaker implantation showed a slight upward trend of the pacing burden and no discernible trend in the intrinsic heart rate (see Figure 12).

[B] The term "inadequate pacemaker dependent rhythm" was assigned to postoperative cardiac rhythms (evaluation upon admission to the intensive care unit) with an intrinsic heart rate below 45 per minute requiring pacing for adequate hemodynamics.

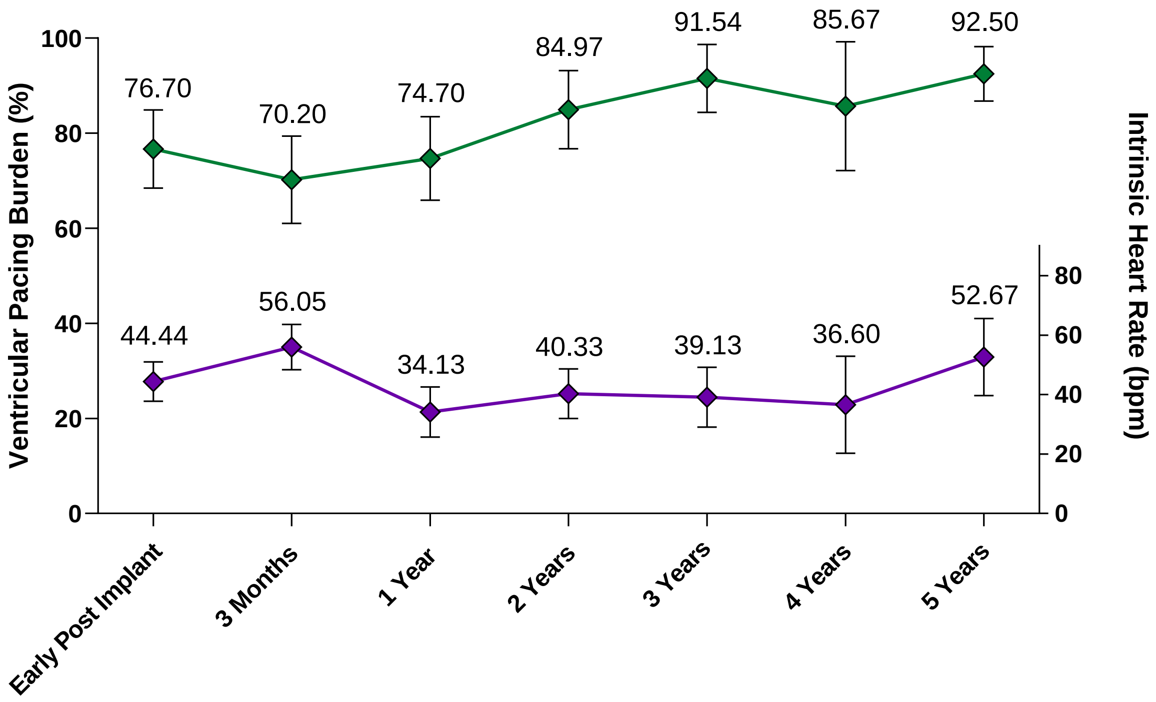


Figure 12 Ventricular pacing burden and intrinsic heart rate of patients who required permanent pacemaker implantation for atrioventricular block after tricuspid valve surgery. Pacing burden was defined as percentage of time paced. Error bars: standard error of the mean.

Figure adapted from Herrmann et al. Atrioventricular block after tricuspid valve surgery. Int Heart J 2021;62(1):57-64 with permission of International Heart Journal. Copyright International Heart Journal 2021. (25)

Survival in Patients with Pacemakers Implanted after Tricuspid Valve Surgery

In the analysis of survival we did not detect a significant difference between patients who required pacemaker implantation for any bradyarrhythmia after tricuspid valve surgery and those who did not require pacemaker implantation (P = 0.751 in the log rank test). Similarly no significant difference was detected when comparing the survival of patients with pacemakers implanted for AVB compared to survival of patients not requiring a pacemaker for AVB (P = 0.604 in the log rank test). Survival was compared using the Kaplan-Meier method making use of landmark methodology.

Conclusion

The anatomic relationship of the tricuspid valve to cardiac conduction tissue puts cardiac conduction tissue at high risk of damage during surgery of the tricuspid valve. Within our complete cohort 77 (15.2%) of the 505 patients underwent pacemaker implantation after surgery. Thirty-three patients (6.5%) underwent pacemaker implantation for AVB. The presence of a pacemaker dependent rhythm directly after surgery and active endocarditis were significant predictors of pacemaker requirement after surgery. Similarly high-grade atrioventricular block directly after surgery and tricuspid valve endocarditis predicted pacemaker requirement for atrioventricular block. The knowledge of these risk factors and of the high rates of bradyarrhythmia in the tricuspid valve patient are highly informative to the cardiac surgeon. Pre- and intraoperative risk assessment can aid in decision-making regarding the implantation of epicardial pacing leads and in postoperative rhythm management.

5. Bradyarrhythmias Related to Mitral Valve Surgery

Introduction

In spite of the rise of the interventional treatment of mitral valve disease (26, 27), mitral valve surgery remains the anatomically most true form of treatment of mitral pathologies. By surgery the precise mechanisms of the mitral pathology can be corrected (Figure 13 and Figure 14). Within the past five decades, mitral valve surgery has undergone a natural evolution with the development of new surgical techniques for repair (28-30) and an expansion of novel surgical access routes (31, 32). Mitral valve surgery will remain the mainstay of the treatment of mitral pathologies and it is important that an understanding of all aspects of this subspecialty be developed. This also pertains to the complications of the procedure as it is with this knowledge that the procedures and the management of the treated patients can be further improved.

Not only does the mitral valve have anatomic relations to conduction tissue, the tricuspid valve, which is frequently concurrently treated, is also in close proximity to conduction tissue (as detailed above). These are key factors putting the conduction tissue at risk during mitral valve surgery. Atrial fibrillation is frequently associated with mitral valve pathologies (33) and concurrent treatment should be considered according to current guidelines (34, 35). Evidence suggests that biatrial ablation procedures increase the risk of bradyarrhythmia after mitral valve surgery (36). Antiarrhythmic medication required for the treatment of atrial fibrillation may further increase this risk.

In our investigation of bradyarrhythmia resulting in pacemaker requirement after mitral valve surgery, we investigated all patients who underwent mitral valve surgery in the Department of Cardiac Surgery, LMU from 2011 until 2014. We investigated a more recent timeframe due to the advances in mitral valve surgery, which have changed the field within the last 2 decades. Our analysis included 797 patients. Patients who had a pacemaker implanted prior to surgery were excluded. We investigated every patient requiring pacemaker implantation after surgery and evaluated predictors of pacemaker requirement.

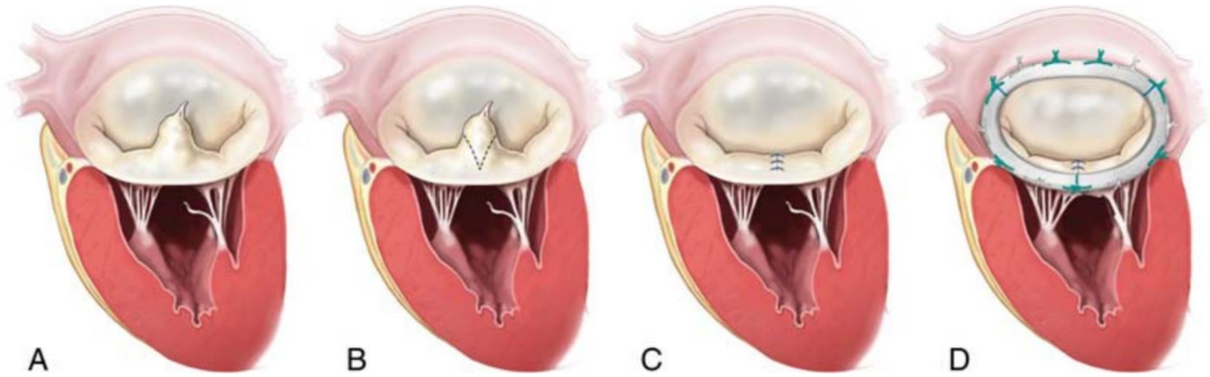


Figure 13 Triangular resection and ring annuloplasty. (A) Fibroelastic deficiency with P2 (posterior middle scallop) prolapse. (B) Dashed lines represent area of leaflet to be excised. (C) Reconstructed leaflet after triangular resection. (D) Completed repair after ring annuloplasty.

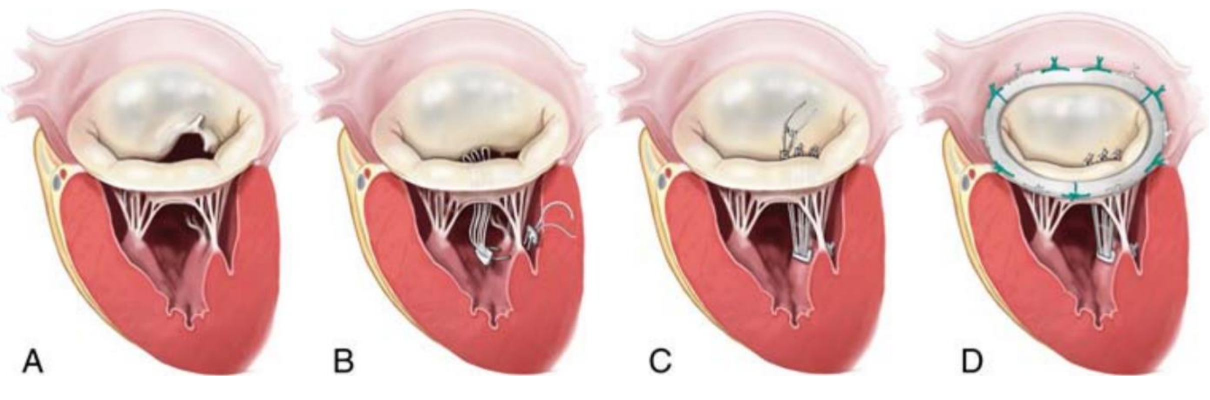
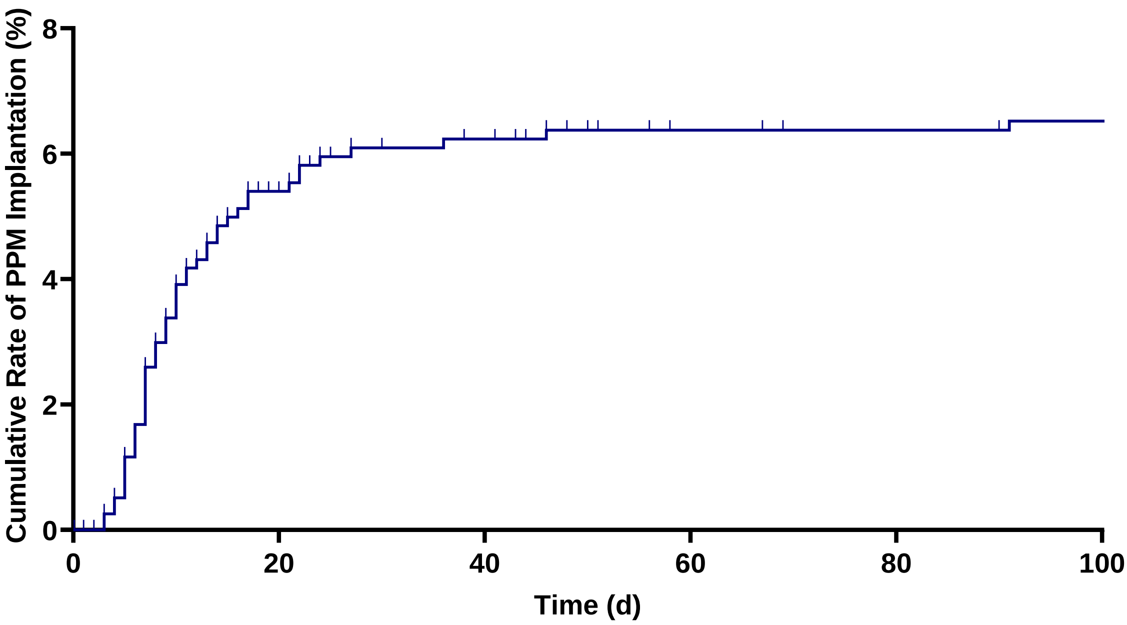


Figure 14 Gore-Tex loop technique and ring annuloplasty. (A) Fibroelastic deficiency with A3 (anterior lateral scallop prolapse). (B) Gore-Tex loops are constructed, and the apparatus is attached to the fibrous tip of the papillary muscle. (C) Individual loops are attached to the prolapsing segment margin. (D) Completed repair after ring annuloplasty.

Pacemaker Implantation Rates

Our complete cohort had a maximum follow-up time of 8.77 years and a median follow-up time of 6.09 years (CI: 5.94–6.22). Throughout follow-up 80 of the 797 patients (10.0%) required pacemaker implantation for bradyarrhythmia.

Time specific pacemaker implantation rates were calculated using the Kaplan-Meier method. This methodology takes into account when patients have deceased and are no longer available for the statistic regarding risk for pacemaker implantation. The following are the pacemaker implantation rates at different points in time after surgery: 6.1% (CI: 4.4 – 7.8) at 1 month, 6.4% (CI: 4.6 – 8.1) at 50 days, 7.8% (CI: 5.9 – 9.8) at 1 year and 12.1% (CI: 9.4 – 14.7) at 8 years. The cumulative rates of permanent pacemaker implantation over time are depicted in Figure 15 below.



No. at Risk

797	686	666	656	654	651

Cumulative Events

0	41	47	48	48	49

Figure 15 Cumulative rate of permanent pacemaker implantation within the first 100 days after mitral valve surgery. PPM: permanent pacemaker; the Kaplan-Meier statistic was used for the generation of this graph.

Figure reproduced from Herrmann et al. Tricuspid valve annuloplasty and mitral valve replacement are associated with bradyarrhythmia after mitral valve surgery. Journal of cardiovascular electrophysiology 2021;32(4):1103-1110 with permission of Wiley Periodicals LLC. Copyright 2021. (37)

Indications for Pacemaker Implantation

Of the 48 patients who had undergone pacemaker implantation within 50 days of surgery 26 (54.2%) suffered from atrioventricular block (AVB), 15 (31.2%) suffered from sinus node dysfunction and 7 (14.6%) from atrial fibrillation with a slow ventricular rate.

Predictors of Pacemaker Implantation

Predictors of pacemaker requirement were investigated based on the patients who required pacemaker implantation within the first 50 days after surgery. Mitral valve replacement (odds ratio: 1.905; CI: 1.206 – 3.536; P = .041) and tricuspid ring annuloplasty (odds ratio: 2.348; CI: 1.165 – 4.730, P = .017) were identified as operative risk factors via multivariable analysis of predictors. Insulin-dependent diabetes mellitus was also identified as a predictor of pacemaker requirement (odds ratio: 4.665; CI: 1.975 – 11.02; P = .001) in multivariable analysis.

Cardiopulmonary bypass time, aortic cross clamp time and reperfusion time were similar in patients who required pacemakers after surgery compared to those who didn't (see Figure 16).

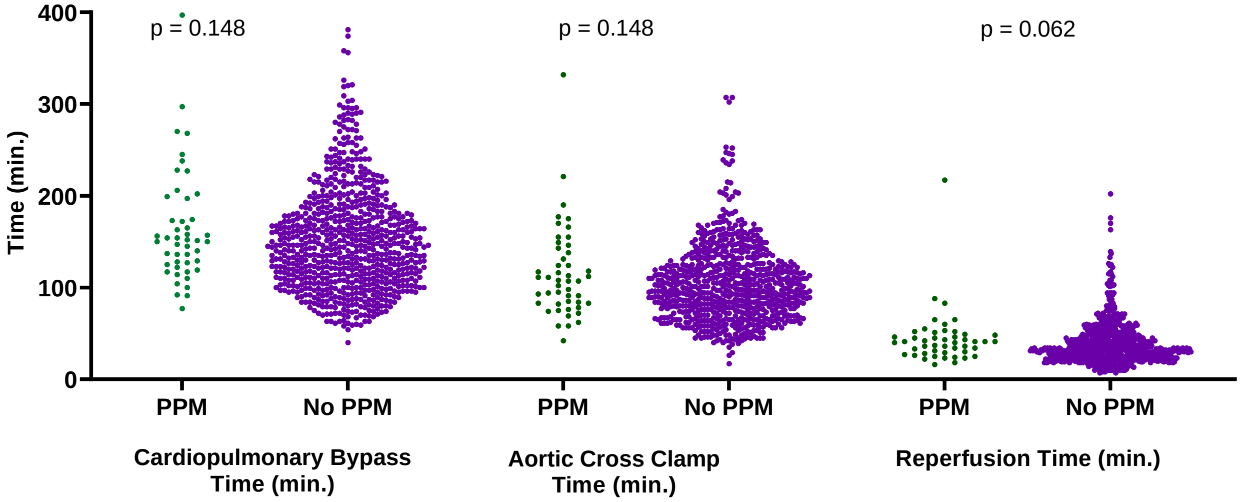


Figure 16 Scatter plots of the cardiopulmonary bypass, aortic cross clamp and reperfusion time during mitral valve surgery with a comparison of patients who required permanent pacemaker implantation after surgery and those who did not require permanent pacemaker implantation. PPM: patients who required permanent pacemakers after surgery; No PPM: patients who didn't require permanent pacemakers after surgery.

Figure reproduced from Herrmann et al. Tricuspid valve annuloplasty and mitral valve replacement are associated with bradyarrhythmia after mitral valve surgery. Journal of cardiovascular electrophysiology 2021;32(4):1103-1110 with permission of Wiley Periodicals LLC. Copyright 2021. (37)

Survival after Surgery

We did not detect a significant difference in the survival of patients who underwent pacemaker implantation after mitral valve surgery compared to patients who did not undergo pacemaker implantation after surgery (P = 0.063 in the log rank test). Survival was compared using the Kaplan-Meier method making use of landmark methodology.

Conclusion

Our analysis showed that the burden of pacemaker requirement after mitral valve surgery is relevant. A higher than expected proportion of patients required pacemaker implantation (6.4% within the first 50 days after surgery). Most patients required pacemaker implantation due to atrioventricular block (54.2 % of the pacemakers implanted within the first 50 days after surgery). We were able to demonstrate that there are two key operative risk factors for pacemaker implantation after mitral valve surgery: mitral valve replacement and concomitant tricuspid valve annuloplasty. Our results have been recently confirmed by the CTSN (Cardiothoracic Surgical Trials Network) *Evaluating the Benefit of Concurrent Tricuspid Valve Repair During Mitral Surgery* trial. The trial also showed that adding tricuspid valve repair to mitral valve surgery relevantly increases the risk of pacemaker implantation (38). It is in our opinion thus critical that the implications of this operative choice always be kept in mind in the planning and in the execution of mitral valve surgery.

6. Complications of Device-Based Bradyarrhythmia Therapy

Introduction

While in the projects presented above the indications and predictors of bradyarrhythmia after cardiac surgery were investigated, the following describes a project devised to quantify and assess the significance of a critical complication of device-based bradyarrhythmia therapy: cardiac implantable electronic device (CIED) infection. The burden of pacemaker therapy does not end with the implantation of the device. After implantation patients remain tied to pacemaker clinics where regular device interrogation and clinical follow-up are essential (39). During follow-up, the treating physicians must be attentive of signs of lead failure, battery depletion but also signs of infection.

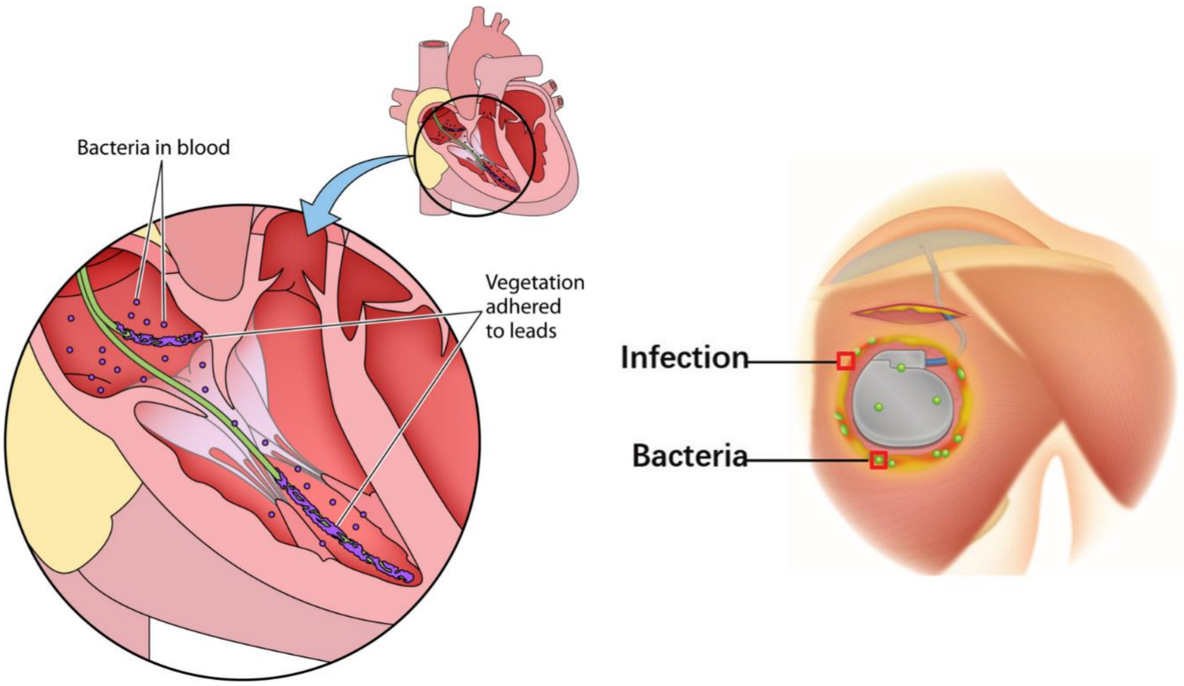


Figure 17 Schematic of the two entities of cardiac implantable electronic device infection. Cardiac implantable electronic device related infective endocarditis on the left and pocket infection on the right.

Figure on the left reproduced from DeSimone et al. Approach to diagnosis of cardiovascular implantable-electronic-device infection. J Clin Microbiol 2018;56(7) with permission of the American Society for Microbiology (ASM), permission conveyed through Copyright Clearance Center, Inc. Copyright ASM 2018. (40) Figure on the right reproduced from Zhang et al. Latex and a zno-based multi-functional material for cardiac implant-related inflammation. Biomater Sci 2019;7(10):4186-4194. with permission of The Royal Society of Chemistry, permission conveyed through Copyright Clearance Center, Inc. Copyright The Royal Society of Chemistry 2019. (41)

Cardiac implantable electronic device infection is the gravest complication of device therapy. Due to persistent microbial infestation conservative treatment without the complete removal of the infected device does not lead to a long term resolution of infection (42) and leads to a high rate of infection relapse (43). Complete device removal is subsequently recommended in all cases of device infection (44-46). In spite of advances in the management of infections and in spite of the implementation of a new consensus statement on lead extraction (44), device infection remains associated with a high mortality and substantial health care costs (47, 48).

In our department CIED infections have been treated since the introduction of pacemaker therapy in the clinical setting. Not only are in-house CIED infections treated, many patients are referred from regional hospitals for the treatment of CIED infection. Subsequently a large knowledge base and extensive clinical experience have been amassed in our institution. It is in an attempt to benefit from this experience that we performed a retrospective analysis of all patients who underwent device removal for CIED infections in our department from 2001 until 2017. The aim of this project was to improve our understanding of when infections develop (related to the time of CIED implantation and the time of the last CIED procedure) and which microorganisms are typically involved in infection. We were furthermore especially interested in predictors of early survival after device removal.

Presentation and Timeline of Infection

In our analysis of 277 patients with CIED infections 148 patients (53.4%) presented with cardiac implantable electronic device related infective endocarditis (CIEDR-IE [C]) and 129 (46.6%) presented with an isolated pocket infections (IPI)[D]. Within our cohort the median age was 73.8 years (IQR: 65.7 - 80.4); 79 patients were female (28.5%). In 172 patients (62.1%) the infected device was a pacemaker, in 44 patients (16%) it was an implantable cardioverter defibrillator, and in 61 patients (22.0%) it was a cardiac resynchronization therapy device with or without defibrillation (CRT - D/CRT - P). The median time since the last CIED procedure was 0.83 years, interquartile range (IQR): 0.25–3.01 years (i.e. 304 days, IQR: 93-1100 days); the median time since initial CIED implant was 4.79 years, IQR: 0.90-11.0 years (i.e. 1748 days; IQR: 325-4015). Temporal data from all patients with CIED infections is presented graphically in
Figure 18.

[C] CIEDR-IE: device infections with signs of local or systemic infection, positive blood cultures, and a vegetation in echocardiography (preferably transesophageal echocardiography).
[D] IPI: device infection with local signs of infection, negative blood cultures and no evidence of a vegetation in echocardiography.

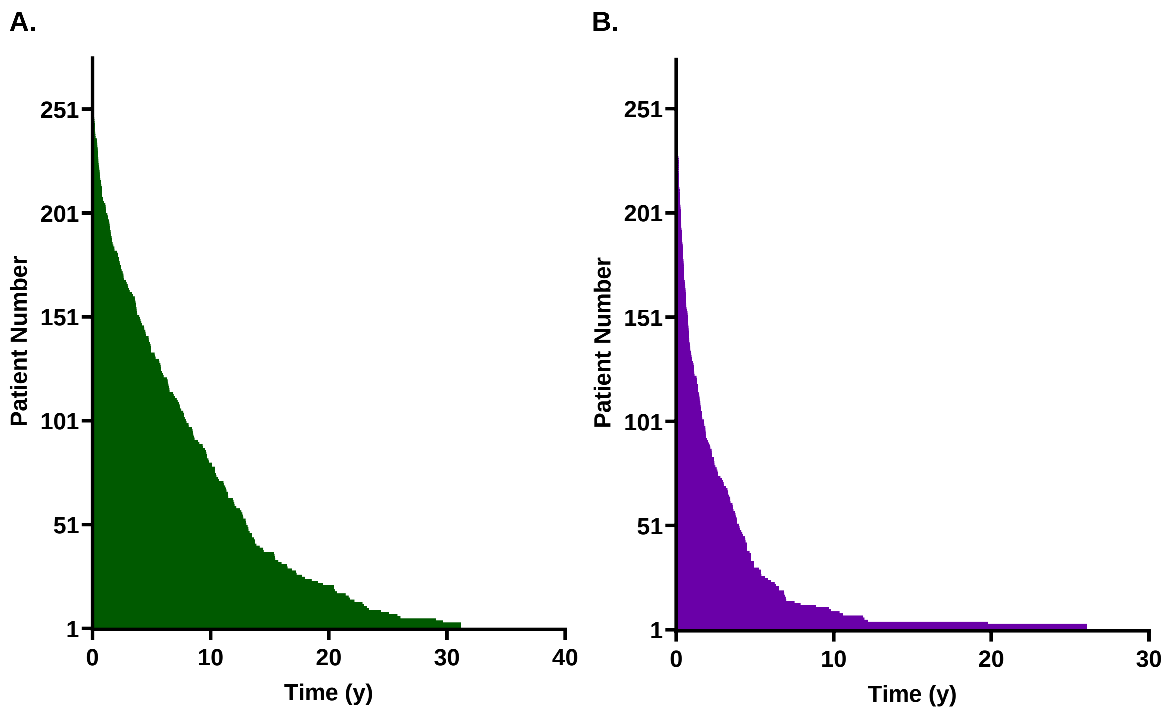


Figure 18 Time from initial cardiac implantable electronic device (CIED) implantation to CIED explantation (A) and time from last CIED procedure to CIED explantation in patients surgically treated for CIED infection.

Figure adapted from Herrmann et al. Thrombocytopenia and end stage renal disease are key predictors of survival in patients with cardiac implantable electronic device infections. Journal of cardiovascular electrophysiology 2020;31(1):70-79 with permission from Wiley Periodicals Inc. Copyright 2019. (49)

Microbiological Isolates

In 114 patients (41.2%) microorganisms were detected in blood cultures. In 183 patients (66.1%) microorganisms were detected in intraoperative material (i.e. generator pocket swab, generator pocket tissue, lead or valve tissue). The most frequently detected microorganisms were *Staphylococus spp.* (including coagulase negative staphylococci and *Staphylococcus aureus*). Further microorganisms detected include *Streptococcus spp.*, *Enterococcus spp.* and Gram-negative bacteria. We did not find a significant difference in patient survival relevant to the type of microorganisms detected. Further details regarding the microbiological results from blood cultures as well as intraoperative material are displayed in Table 2.

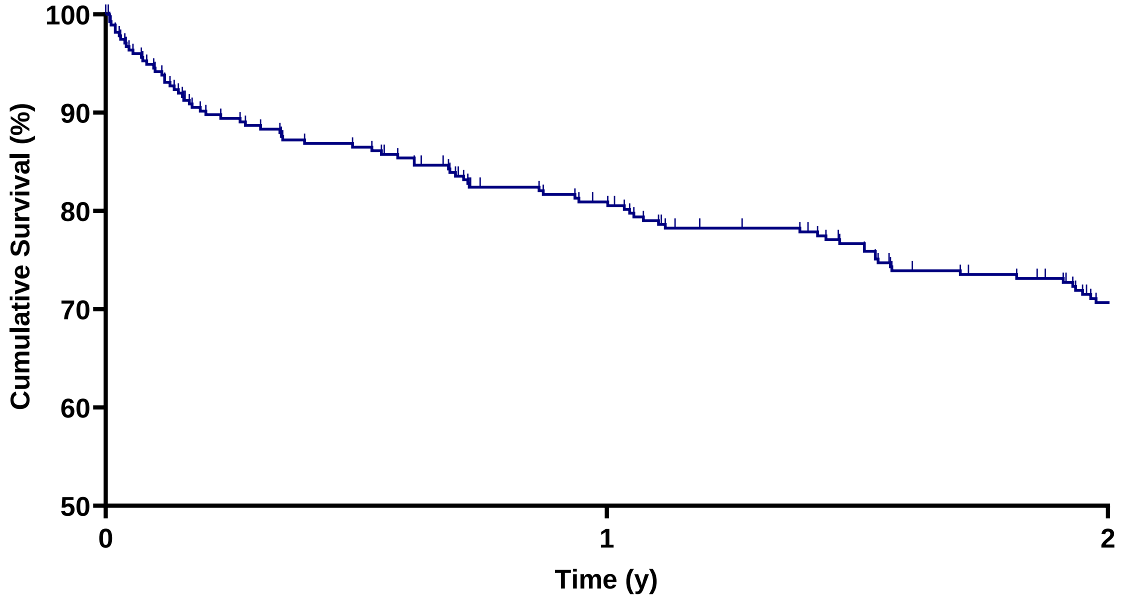
Microbiological Results	Blood Culture	Intraoperative Material
Staphylococcus spp.	83 (72.8 %)	124 (67.8 %)
Coagulase negative staphylococci	30 (26.3 %)	86 (47.0 %)
Staphylococcus aureus	53 (46.5 %)	38 (20.8 %)
Streptococcus spp.	6 (5.3 %)	4 (2.2 %)
Enterococcus spp.	9 (7.9 %)	6 (3.3 %)
Gram Negative	4 (3.5 %)	4 (2.2 %)
Other	2 (1.8 %)	11 (6.0 %)
Polymicrobial	10 (8.8 %)	34 (18.6 %)
Total	114 (100.0 %)	183 (100.0 %)
	Blood Culture	Intraoperative Material
Total cases with positive microbiological isolates (out of total cases)	114 (41.2 %)	183 (66.1 %)
Total cases without positive microbiological isolates (out of total cases)	163 (58.8 %)	94 (33.9 %)

Table 2 Microbiological results depending on source material investigated in patients surgically treated for cardiac implantable electronic device infections. Intraoperative material includes generator pocket swab, generator pocket tissue, lead or valve tissue.

Table adapted from Herrmann et al. Thrombocytopenia and end stage renal disease are key predictors of survival in patients with cardiac implantable electronic device infections. Journal of cardiovascular electrophysiology 2020;31(1):70-79 with permission from Wiley Periodicals Inc. Copyright 2019. (49)

Survival and Predictors of Survival

Thirty day survival was 94.9% (CI: 92.3 – 97.5) and 1 year survival was 80.9% (CI: 76.4 – 85.7). Kaplan-Meier estimates of survival within 2 years and 10 years after surgical treatment of CIED infections are graphed in Figure 19 and Figure 20 respectively. In multivariable analysis, we identified age (odds ratio: 1.05; CI: 1.01 – 1.09; P = 0.009), end stage renal disease (ESRD) with dialysis (odds ratio: 5.14; CI: 1.87 – 14.11; P = .001), positive blood cultures (odds ratio: 2.19; CI: 1.08 – 4.45; P = .030) and thrombocytopenia (odds ratio: 2.3; CI, 1.03 – 5.15; P = .042) as significant predictors of 1 year mortality after surgical treatment of CIED infection.



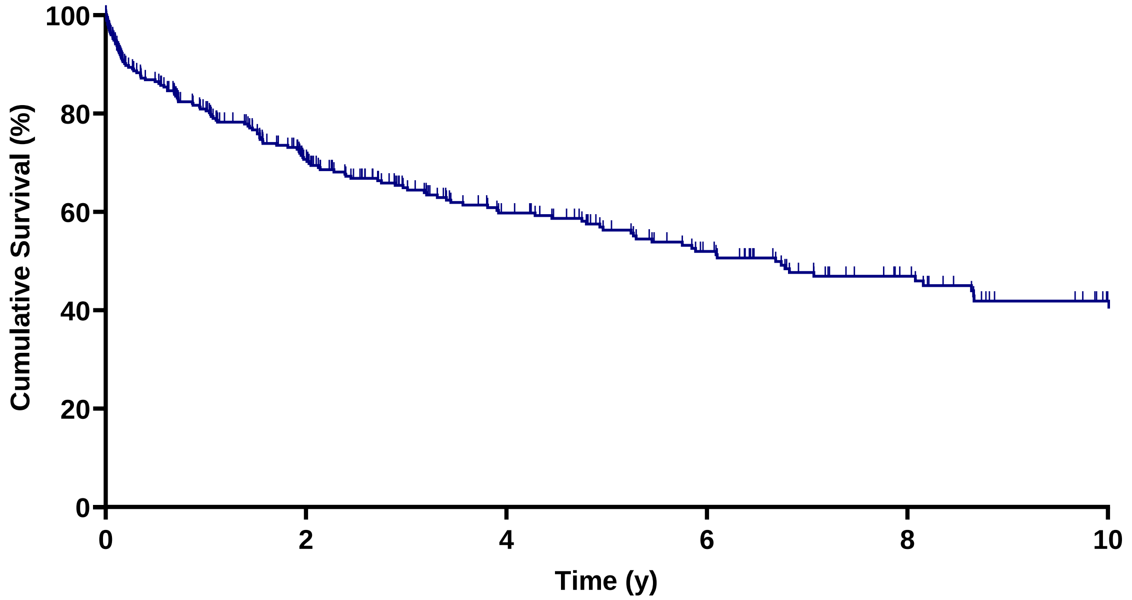
No. at Risk

277	215	172

Cumulative Events

0	52	78

Figure 19 Survival within the first 2 years after surgical treatment of cardiac implantable electronic device infection.



No. at Risk

277	172	112	80	51	27

Cumulative Events

0	78	101	114	121	126

Figure 20 Survival within the first 10 years after surgical treatment of cardiac implantable electronic device infection.

Conclusion

In this in-depth investigation of our departments 17 year experience with the treatment of CIED infections we identified a high 1 year mortality (19.1%) – as has been previously reported. Within our cohort we were able to identify key predictors of 1-year mortality. We found that patients with end stage renal disease and patients with thrombocytopenia are at a high risk of mortality during the treatment of CIED infections. Further predictors of survival were the presence of bacteria in blood cultures and advanced age. These insights provide a jumping-off point for the possible development of risk based treatment strategies for the treatment of CIED infection.

7. Tachyarrhythmia after Cardiac Surgery

Introduction

While bradyarrhythmia after cardiac surgery can result in patients requiring the implantation of a permanent pacemaker, postoperative tachyarrhythmia can result in patients requiring further rhythm stabilizing medication and possibly even long-term anticoagulant therapy (35). Postoperative tachyarrhythmia most frequently constitutes atrial fibrillation (AF) and has previously been found to have a high incidence in the first postoperative week after cardiac surgery (2). In patients undergoing coronary artery bypass grafting, the reported postoperative incidence is ~29% (50-52). In patients receiving valvular surgery, and especially combined surgical procedures, even higher rates have been reported (2).

Postoperative atrial fibrillation is associated with an increase in morbidity and mortality after cardiac surgery (53, 54). This is the central fact which makes research in this field so important. Several areas within this field require further intensive research. The pathophysiology of an increased mortality in patients with temporary AF after surgery remains to be understood, strategies for a reduction of the burden of AF after surgery remain to be developed and the natural development of the atrial fibrillation after surgery remains to be uncovered.

The aim of the study presented below was to investigate the natural development of atrial fibrillation after cardiac surgery. Recent studies have shown that an investigation and quantification of atrial fibrillation is only reliably feasible making use of data from continuous rhythm monitoring devices such as CIEDs (55-57). This study sums up the complete rhythm history of 426 patients with a history of cardiac surgery who participated in the OMNI[E] (58) and TRENDS[F] (59) multicenter trials. Atrial lead data from permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD) was reconstructed. The data was analyzed to investigate the recurrence patterns of atrial fibrillation which was detected in the form of atrial high-rate episodes (see Figure 21). Furthermore factors affecting the length of AF episodes as well as spontaneous conversion of AF to sinus rhythm were investigated.

[E] OMNI is a multicenter, nonrandomized, observational study of pacemaker, ICD and cardiac resynchronization therapy utilization.
[F] TRENDS is a multicenter, nonrandomized, observational study investigating atrial arrhythmias through continuous data collection by pacemakers, ICDs, and cardiac resynchronization devices.

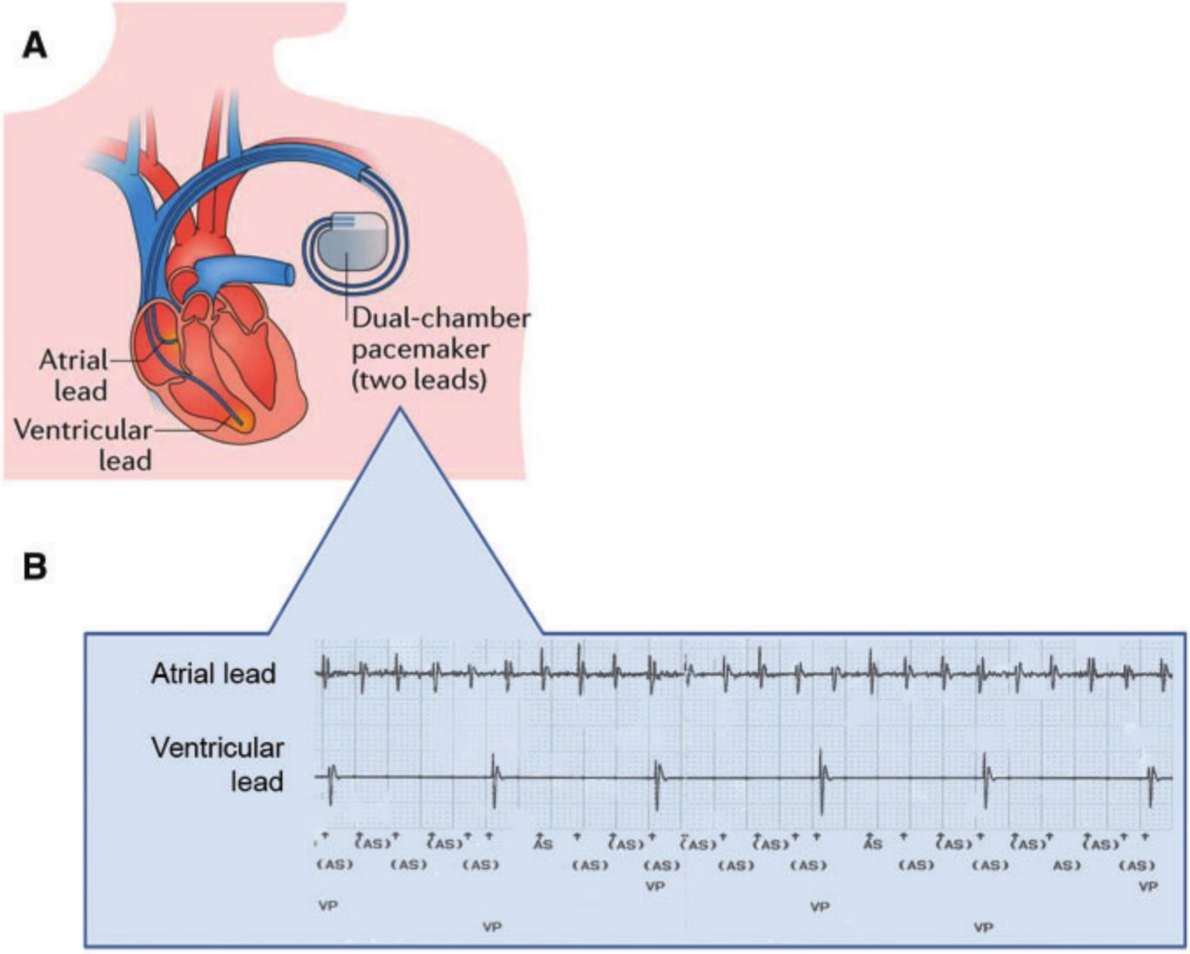


Figure 21 Detection of atrial high rate episodes using cardiac implantable electronic devices. A. Dual-chamber pacemaker with a right atrial and a right ventricular lead. B. Atrial and ventricular electrograms detected by the device. Atrial high rate episodes such as the one depicted in the upper tracing in most cases represent atrial fibrillation or atrial tachyarrhythmias. AS, atrial sensing; VP, ventricular pacing.

Adapted from Freedman et al. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. Nat Rev Cardiol 2017;14(12):701-714 with permission from Macmillan Publishers Ltd: Nature Reviews Cardiology; doi: 10.1038/nrcardio.2017.94. Copyright 2017. (60) and from Uittenbogaart et al. Burden of atrial high-rate episodes and risk of stroke: A systematic review. Europace 2018;20(9):1420-1427 by permission of Oxford University Press and the European Society of Cardiology. Copyright 2017. (61)

Atrial Fibrillation Burden and Density

Within the investigated cohort 320 patients were found to have atrial fibrillation during the timeframe investigated. The mean follow-up was 351 days. The mean burden of AF was 21% (see Figure 22). In most patients high density AF was detected (AF density: 0.78, standard deviation (SD) 0.23). The mean episode length was 5.9 days with a vast majority of episodes having a length of 1 day (see Figure 22).

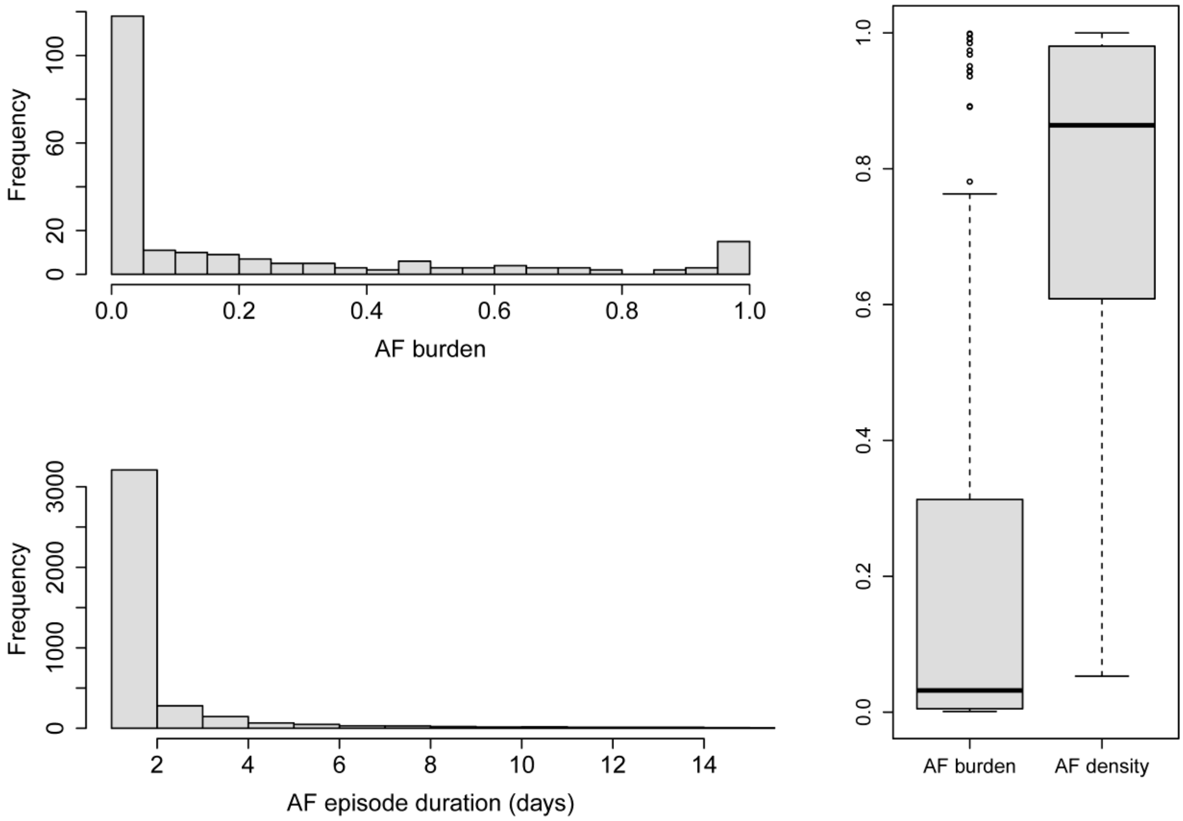


Figure 22 Depiction of atrial fibrillation burden and atrial fibrillation density in patients developing atrial fibrillation after cardiac surgery.

Figure reproduced from Charitos et al. Atrial fibrillation recurrence and spontaneous conversion to sinus rhythm after cardiac surgery: Insights from 426 patients with continuous rhythm monitoring. Journal of cardiovascular electrophysiology 2021;32(8):2171-2178 with permission from Wiley Periodicals LLC. Copyright 2021. (62)

Predictors of AF Episode Duration

Poisson regression modeling resulted in the detection of several predictors significantly associated with AF episode duration. These factors were: history of coronary artery disease (estimate 0.83; CI: 0.72 – 0.95; P = 0.006), history of myocardial infarction (estimate 1.15; CI: 1.06 – 1.26; P = 0.001), diabetes (estimate 1.11; CI: 1.02 – 1.21; P = 0.022), atrial fibrillation burden (estimate 11.82; CI: 10.27 – 13.59; P < 0.001), aortic valve surgery (estimate 1.27; CI: 1.14 – 1.41; P < 0.001), mitral valve surgery (estimate 1.13; CI: 1.00 – 1.28; P = 0.043).

Probability of Spontaneous AF Conversion to Sinus Rhythm

Within the population investigated a reduction in the probability of spontaneous conversion of AF to sinus rhythm was detected the longer a patient remained in AF. The reduction in the rate of spontaneous conversion reached a plateau at 5-7 days in atrial fibrillation (Figure 23).

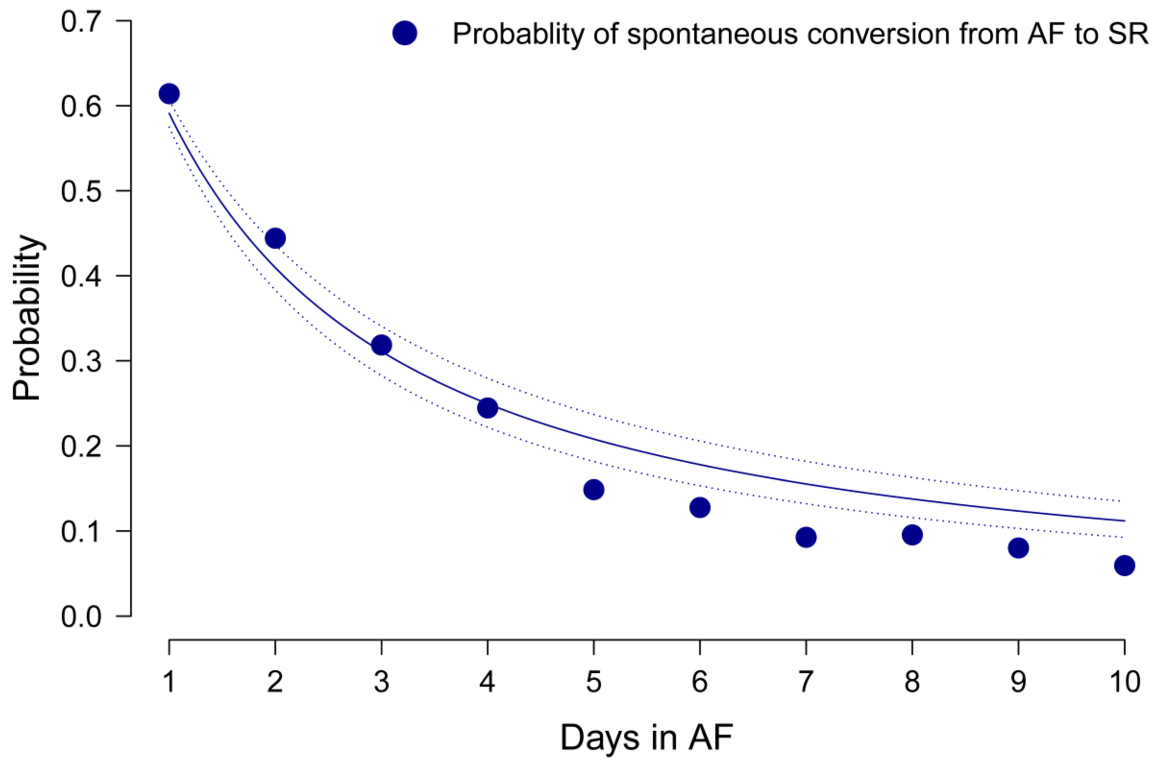


Figure 23 Graphical depiction of spontaneous probability of conversion of atrial fibrillation to sinus rhythm after cardiac surgery related to number of days spent in atrial fibrillation.

Figure reproduced from Charitos et al. Atrial fibrillation recurrence and spontaneous conversion to sinus rhythm after cardiac surgery: Insights from 426 patients with continuous rhythm monitoring. Journal of cardiovascular electrophysiology 2021;32(8):2171-2178 with permission from Wiley Periodicals LLC. Copyright 2021. (62)

Predictors of the Probability of Spontaneous AF Conversion to Sinus Rhythm

Predictors of the probability of spontaneous conversion of AF to sinus rhythm were investigated by multivariable regression modelling. Both AF density and AF burden significantly affected the probability of spontaneous conversion. The initial probability of AF conversion was significantly higher with a higher AF density and significantly lower with an increased AF burden. The initial probability of spontaneous conversion was also significantly increased in patients of higher age and in patients with coronary artery disease.

Conclusion

Atrial fibrillation is very common among patients who have undergone cardiac surgery. In the investigated cohort it could be determined that low-burden, high-density atrial fibrillation is the most common form in this patient group. While atrial fibrillation typically spontaneously converts to sinus rhythm the probability of conversion sinks with increased time spent in AF. Further patient related and procedure related factors affect the length of episodes and the rate of conversion. One clear take-home message of this investigation is that continuous monitoring data has a great potential to facilitate an expansion of our knowledge base regarding atrial fibrillation after cardiac surgery. It is crucial that such strategies be applied in future investigations.

8. Perspective

Above a multi-project, long-term effort to understand the burden of arrhythmias after cardiac surgery was presented. With an investigation of bradyarrhythmias after heart transplantation, after tricuspid valve and mitral valve surgery an attempt was made at informing clinicians regarding truly relevant postoperative conditions which deserve attention and respect. Each individual project resulted in knowledge, which can aid the physician in clinical decision-making regarding the choice to implant a pacemaker, the timing of pacemaker implantation and even the choice to implant an epicardial pacemaker lead during cardiac surgery.

In a further project, supporting PD Dr. Efstratios Charitos, an eminent researcher in the field of AF research, postoperative atrial fibrillation after cardiac surgery was investigated. Along with insights on the burden and predictors of atrial fibrillation after cardiac surgery a key insight provided by the study was that continuous rhythm monitoring will be a central component of future arrhythmia research. It is based on this understanding that we have devised the CABG-AF study at the Ludwig Maximilian University.

The CABG-AF study[G] is a prospective observational study investigating the true incidence of post coronary artery bypass grafting (CABG) atrial fibrillation and characterizing postoperative AF patterns in patients who prior to surgery had no history of arrhythmias. Insertable cardiac monitors will be implanted at the end of CABG and electrocardiographic data will be collected continuously. The data collected will provide insights on the primary endpoint: incidence of AF, as well as secondary endpoints such as AF burden and density. This is a novel study format, which has the potential to provide extensive insights in this field. Subsequently we expect a further advancement of understanding in the field of arrhythmias after cardiac surgery through such work.

A scientific pathway through multiple projects presented above has led to the experience and knowledge required for the initiation of our CABG-AF study. It is through such modern forms of data collection that scientific research in the field of *arrhythmia after cardiac surgery* can be advance. It is our hope that the insights gained will subsequently allow an improvement of patient care.

[G] CABG-AF: Characterization of Post Coronary Artery Bypass Grafting Atrial Fibrillation Patterns

9. Abbreviations

AF: atrial fibrillation

AVB: atrioventricular block

CABG: coronary artery bypass grafting

CABG-AF: Characterization of Post Coronary Artery Bypass Grafting Atrial Fibrillation Patterns

CI: 95 % confidence interval

CIED: cardiac implantable electronic device

CIEDR-IE: cardiac implantable electronic device related infective endocarditis

ESRD: end-stage renal disease

ICD: implantable cardioverter defibrillators

ICU: intensive care unit

IPI: isolated pocket infection

IQR: interquartile range

LMU: Ludwig Maximilian University, Munich

PPM: permanent pacemaker

SD: standard deviation

SE: standard error of the mean

SND: sinus node dysfunction

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