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DISSERTATION

Influence of Right Ventricular Leads of Cardiac Devices on Tricuspid Valve Function and Occurrence of Tricuspid Regurgitation

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List of Abbreviations

AF: atrial fibrillation
AV-Block: atrioventricular conduction block
BPEG: British Pacing and Electrophysiology Group
CRT: cardiac resynchronization therapy
CVP: central venous pressure
CCT: contractility modulation
ECG: electrocardiogram
EROA: effective regurgitant orrifice area
HF: heart failure
ICD: implantable cardioverter defibrillator
IQR: interquartile range
LA: left atrium
LHF: left heart failure
LVEF: left ventricular ejection fraction
TR Vmax: maximum tricuspid regurgitation velocity in m/sec
mmHg: millimeters of mercury
NYHA: New York Heart Association
NASPE: North American Society of Pacing and Electrophysiology
PM: pacemaker
PISA: proximal isovelocity hemispheric surface area
PAP: pulmonary arterial pressure
R vol: regurgitant volume
RA: right atrium
RHF: right heart failure
RV: right ventricle
SSS: Sick Sinus Syndrome
SD: standard deviation
SPAP: systolic pulmonary artery pressure
TR Vmax: TR maximum jet velocity
TEE: transesophageal echocardiography
TTE: transthoracic echogardiography
TAPSE: tricuspid annular plane systolic excursion
TR: tricuspid regurgitation
TV: tricuspid valve
VHD: valvular heart diseases
VF: ventricular fibrillation
VT: ventricular tachycardia
WHO: World Health Organization

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Abstract English

Introduction: In Germany, many Pacemakers (PM) and cardiac rhythm devices are implanted at specialized clinics each year. However, the impact of right ventricular leads on the tricuspid valve (TV) function as well as possible effects on mortality are largely unexamined. Previous studies show heterogeneous results. This study aims at investigating whether the presence of right ventricular PM leads influences TV function.

Methods: The study was conducted retrospectively at the Charité Universitätsmedizin Berlin and included a total of 261 patients, of whom 123 had undergone cardiac device implantation between 2010 and 2016 (PM group), and 138 controls. An initial transthoracic echocardiography (TTE), and up to three follow-up TTEs at one month, 12 months and after a minimum of one year were evaluated for each patient. Primary outcome was the Grade of Tricuspid Regurgitation (TR). Additional secondary parameters were: TR Vmax, tricuspid annular plane systolic excursion (TAPSE), left ventricular ejection fraction (LVEF), systolic pulmonary artery pressure (SPAP), central venous pressure (CVP), vena contracta width, proximal isovelocity surface area (PISA) and right atrium volume (RA Vol). The cumulative survival probability for both groups was analyzed using the Kaplan- Meier Estimate.

Results: The pacemaker group's median TR Grading was significantly greater initially and long-term than that of the control group ($p=0.024$ and $p=<0.001$). TR Grading worsened long-term more often in the PM group (N=34, 44%) than in the control group (N=23, 27%). The PM group's overall left-heart function (LVEF) was significantly lower at all examination periods ($p=$always <0.005) and the right heart function (TAPSE) was almost always significantly worse ($p=<0.05$ for initial, mid- and long-term examination). Both parameters remained stable over time. The PM group's mean RA Vol was significantly greater initially ($p=0.018$), however no great change was observed by the end of this study. Results pertaining to SPAP, vena contracta and PISA showed no disparities between groups. The PM group had a significantly lower probability of cumulative survival ($p=0.016$).

Conclusion: Patients with a cardiac rhythm device had overall worse parameters pertaining to TV function and right and left heart function. However, most of these parameters did not majorly fluctuate or aggravate over time thus suggesting that the presence of an RV lead does not influence TV function. Additionally, this study implies that patients with a PM have a higher mortality.

Abstract Deutsch

Einleitung: Jedes Jahr werden in Deutschland viele Aggregate im Rahmen des Herz-Rhythmus Managements in spezialisierten Kliniken implantiert. Die möglichen Auswirkungen einer rechtventrikulären Sonde auf die Trikuspidalklappen (TK) Funktion und auf die Mortalität ist jedoch noch weitestgehend unerforscht. Frühere Studie zeigten heterogene Ergebnisse. Ziel dieser Studie ist es, zu untersuchen, ob das Vorhandensein einer rechtsventrikulären Sonde die TK Funktion beeinflusst.

Methoden: Die vorliegende Studie wurde retrospektiv an der Charité Universitätsmedizin Berlin durchgeführt und umfasste insgesamt 261 Patienten, von denen 123 Patienten von 2010 bis 2016 ein Herz-Rhythmus-Gerät implantiert wurde (Schrittmacher (SM) Gruppe), sowie 138 Kontrollen. Eine initiale transthorakale Echokardiographie (TTE) und bis zu drei nachfolgende TTEs innerhalb eines Monats, 12 Monaten und nach mindestens einem Jahr wurden für jeden Patienten ausgewertet. Der primäre Parameter war der Grad der trikuspidalen Insuffizienz (TI). Die zusätzlichen sekundären Parameter wurden erfasst: TI Vmax, „tricuspid annular plane systolic excursion“ (TAPSE: ein Wert, der für die Beurteilung der allgemeinen Rechtsherzfunktion herangezogen wird), linksventrikuläre Ejektionsfraktion (LVEF), systolischer Pulmonalarteriendruck (SPAP), zentral venöser Druck, vena contracta Weite, „proximal isovelocity surface area“ (PISA) und rechtes Vorhofvolumen (RA Vol). Die kumulative Überlebenswahrscheinlichkeit für beide Gruppen wurde mit Hilfe der Kaplan-Meier-Schätzung analysiert.

Ergebnisse:

Die mediane TI-Graduierung der SM Gruppe war anfänglich und langfristig signifikant höher als die der Kontrollgruppe (p=0,024 und p=<0,001). Die TI-Graduierung verschlechterte sich in der SM Gruppe (N=34, 44%) langfristig häufiger als in der Kontrollgruppe (N=23, 27%). Die Gesamtfunktion des linken Herzens (LVEF) war zu allen Untersuchungszeitpunkten signifikant geringer (p=immer <0,005) und die Funktion des rechten Herzens (TAPSE) fast immer signifikant schlechter (p=<0,05 für Initial-, Mittel- und Langzeituntersuchungen) in der SM Gruppe. Beide Parameter blieben im Laufe der Zeit stabil. Das RA Vol der SM Gruppe war inital signifikant größer (p=0,018), jedoch wurde am Ende dieser Studie keine große Veränderung beobachtet. Die Ergebnisse zu SPAP, vena contracta und PISA zeigten keine

Unterschiede zwischen den Gruppen. Die PM-Gruppe hatte eine signifikant geringere Wahrscheinlichkeit für das kumulative Überleben (p=0,016).

Zusammenfassung: Patienten mit einem SM oder andere Aggregate hatten insgesamt schlechtere Parameter in Bezug auf die TV-Funktion, sowie auf die rechte und linke Herzfunktion. Die meisten dieser Parameter schwankten oder veränderten sich jedoch nicht wesentlich im Laufe der Zeit, was darauf hindeutet, dass das Vorhandensein einer rechtsventrikulären Sonde die TK Funktion nicht beeinflusst. Allerdings impliziert diese Studie, dass Patienten mit einem SM eine höhere Sterblichkeitsrate aufweisen.

Introduction

1. 1. The First Pacemakers

The earliest attempts at devising pacemakers (PM) took place in the 1930s when Albert Hyman created the so-called Hyman Oter[3,4]. Roughly two decades later, the first devices similar to those today were developed concurrently in the USA and Europe, mainly in Sweden[5]. In 1952 the cardiologist Paul Zoll designed an external PM[4] and in 1956, the American Engineer Wilson Greatbatch and Andrew Gage developed the first PM with mercury zinc batteries[4]. In 1957 Vincent Gott, John Johnson and Clarence W. Lillehei came together and constructed a temporary cardiac pacer[3,5]. It was also Lillehei who instructed the engineer Earl Bakken to create a permanent construction[3]. The engineer Rune Elmqvist in Sweden designed a PM that same year[5]. Even though there are many individuals associated with the development of PMs coincidently, it is necessary to name all of them as each person contributed separately to a specific mechanical feature. There were many differences concerning the battery composition, battery life, polarity and general design[3,6].

Despite the technical differences across the globe, the first permanent implantations of a PM in humans occurred parallel and under similar circumstances. In 1958 in Stockholm Elmqvist together with the Swedish Surgeon Åke Senning implanted the first PM into a human, who had suffered from complete heart block and consequently Adam-Stokes attacks[3,5]. This patient continued to live for 43 years and died of an unrelated cause[4]. Briefly thereafter in 1960, William Chadack implanted the first PM designed by Greatbatch in Buffalo New York. The patient was 77 years old and also suffered from symptomatic complete AV Block[3]. The outcome of this specific patient is unknown, however the following implantations demonstrated that Greatbatch's PM had a lifespan of one to five years[3].

After a whirlwind of PM engineering and experimenting within the one decade, the ones afterwards concentrated on solving the problems concerning battery life and materials used in the devices. Chadack and Elmqvuist are only exemplary and the most renown amongst the many people involved and attempts that took place over time during the evolution of PMs. John Schwedel, Seymour Furman, William Glenn and Alexander Mauro in the USA, Robert Rubio in Uruguay, Lagergran in Sweden and Mohammed Khalilullah in India are few examples of individuals who had contributed to their evolution as well[4].

1. 2. The Modern Pacemaker

1. 2. 1. Cardiac Electrical Conduction System

In order to understand how a PM or a similar device works, one must understand how the heart's own natural electrical conducting system works and what types of illnesses they can be used for.

Image 1: Electrical Conduction System of the Heart[2]

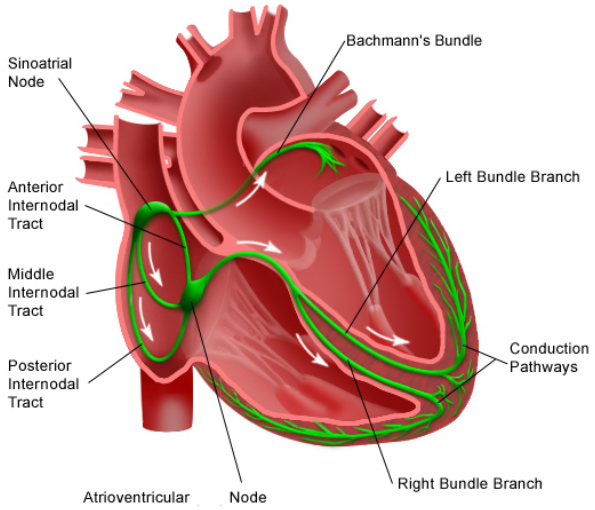


Image 1: the anatomical electrical conducting system of the heart, here marked in green. The image is from the Stanford Children's' Hospital website[2].

Generally speaking, the conduction system of the heart allows signals to spread across the heart enabling it to contract as a muscle in an organized manner[7]. Physiologically the initial action potential starts in the sinoatrial node, which is located in the upper right posterior part of the right atrium (RA),. The sinoatrial node creates action potential autonomously with an underlying heart frequency of around 60 to 100 beats per minute. From here on, the action potential spreads across the RA via three internodal tracts and is thought to spread to the left atrium (LA) via the Bachmann's Bundle. It then arrives at the Atrioventricular node, located at the interatrial septum. Only after a certain delay does the action potential spread to the His Bundle and to its right and left bundle branches. Labeled in Image 1 as "Conduction Pathways" are the Purkinje Fibers, leading the action potential into the myocardial muscle tissue[7,8].

1. 2. 2. Cardiac Arrhythmias and Desynchronized Heart Function

The type of arrhythmia depends on where the problem or disruption within the electrical conducting system or myocardia is located. Principally arrhythmias can be divided in to bradycardia with a heart rate below 60 beats per minute and tachycardia, with a heart rate above 100 beats per minute. Additionally, most arrhythmias can be idiopathic or caused by pre-existing cardiac damage leading to fibrosis or myocarditis, such as an occurred myocardial infarction, infection, congenital circumstances, cardiomyopathy, arterial hypertension or coronary artery disease[7-10].

Sick Sinus Syndrome (SSS) summarizes a group of illnesses that cause dysfunction in the sinus node and encompasses many symptoms, including both brady- as well as tachycardia. It can appear as sinus bradycardia, which is when the sinus node itself doesn't create enough action potential and thus heart contractions per minute. Sinus pauses of over 3 seconds can occur as well. Lastly, bradycardia-tachycardia syndrome is a condition in which both heart rate pathologies occur alternately[7,8].

Atrioventricular Conduction Block (AV-Block) is an illness, in which the transmission of action potential from the atria to the His Bundle is delayed or entirely prevented due to damage in either location. First degree AV-Block is when the PQ-interval is always over 200ms but doesn't alter in length at any given time. Most of these patients are not symptomatic. Second degree AV-Block is divided into Mobitz Type I and Type II. Type I is when the PQ-interval repeatedly gradually gets longer until there is no contraction after a p-wave. Type II is when a contraction repeatedly does not occur after p-wave, but the PR-interval remains constant. At this point patients can become symptomatic. Third degree AV-Block is almost always symptomatic, as there is no conduction between the atria and His Bundle at all anymore. In this case, the His Bundle can create an autonomous frequency of about 40 beats per minute on its own. However, a third degree AV-Block can cause such a haemodynamic disruption, that a patient can suffer a syncope, then also called Adam Stokes Attack. All AV-Blocks are categorized as bradycardia[7,8,11]. Furthermore, AV-Blocks can principally be described as having an intrinsic or extrinsic cause. Intrinsic means, the AV-Block is due to a problem within the heart itself, such mechanisms are mostly connected to Adam Stokes Attacks. Extrinsic means the cause is elsewhere: either due to parasympathetical vagal nerve dysregulation, linked to the development of reflex strokes, "is associated with low levels of endogenous adenosine and is supposed to be

one of the mechanisms involved in low-adenosine syncope“[12], or can be a manifestion of a complication of other diseases such as Lyme carditis[13].

Tachycardia can be attributed to problems in the atria or ventricles. Atrial Fibrillation (AF) is one of the most common arrhythmias. In Germany alone it is diagnosed in 10% of patients over the age of 80 years[14] and worldwide “the current estimate of the prevalence of AF in the developed world is approximately 1.5-2% of the general population”[15]. AF is when undirected excitation occurs across the atria causing uncoordinated contractions of the atria. This leads to the irregular conduction of impulses to the ventricles, causing a heart rate of up to 300-600 beats per minute, also called tachycardia absoluta. In some cases, impulses are conducted so unregularly and unreliably, that it induces a paradox bradycardia absoluta[7,8].

A re-entry mechanism is an electrical impulse that gets conducted over and over again at a specific location in the myocardia or conduction system. This can happen when a short circuit develops because a branch in the conduction system is blocked or damaged. Re-Entry can cause tachycardia in the atria as well as in ventricles and can be paroxysmal[7,8,16].

Ventricular tachycardia (VT) is a general term used to describe when tachycardia is due to problems in the ventricles. Apart from re-entry mechanisms, there are two other special forms of tachycardia worth mentioning: ventricular fibrillation (VF) and torsade de pointes. VF is when there is an undirected and completely unorganized contraction of the ventricles up to 400 beats per minute causing death. Torsade de pointe is seen as state of transition into VF but can also sustain spontaneously and is characterized by a specific pattern in an electrocardiogram (ECG) known as its translation “twisting of the peaks”. [7,8,17].

Not only cardiac arrhythmias induce uncoordinated cardiac contraction. For example, the right or left bundle branch conduction can be compromised. A blockage leads to the muscle tissue it activates not contracting anymore. If a patient suffers from an underlying heart disease or if more than one branch is affected, the heart’s contraction can be severely impaired, even inducing heart failure (HF). However, the right bundle block is more likely to be less symptomatic, as the right ventricle (RV) can still be activated by the left branch. Additionally, the left bundle branch block occurs more often due to degenerative diseases or damage caused by prior myocardia infarcts, but in both cases congenital blocks can occur.[7,9,11,18].

1. 2. 3. Heart Rhythm Devices and their Indications

There are several types of devices used for cardiac pacing. Which device is implanted depends on the indication or rather which underlying heart rhythm disturbances or dysfunctions have been diagnosed.

1. 2. 3. 1. Pacemaker

First and foremost there is the PM, which basically is an electrical device that sends electrical impulses to the heart either causing it to contract faster or slower. As shown below (Image 2), the small generator is usually placed subcutaneously under the collarbone. There are leads attached to it, which connect the electrodes at the end of them to the generator. They are inserted via the subclavian vein and are pushed forward through the superior vena cave and enter the heart via the RA and pushed further through the tricuspid valve (TV) into the RV if necessary. The electrodes are then positioned into the heart wall of the chamber they are in[19-22].

Image 2: Dual Chamber Pacemaker[19]

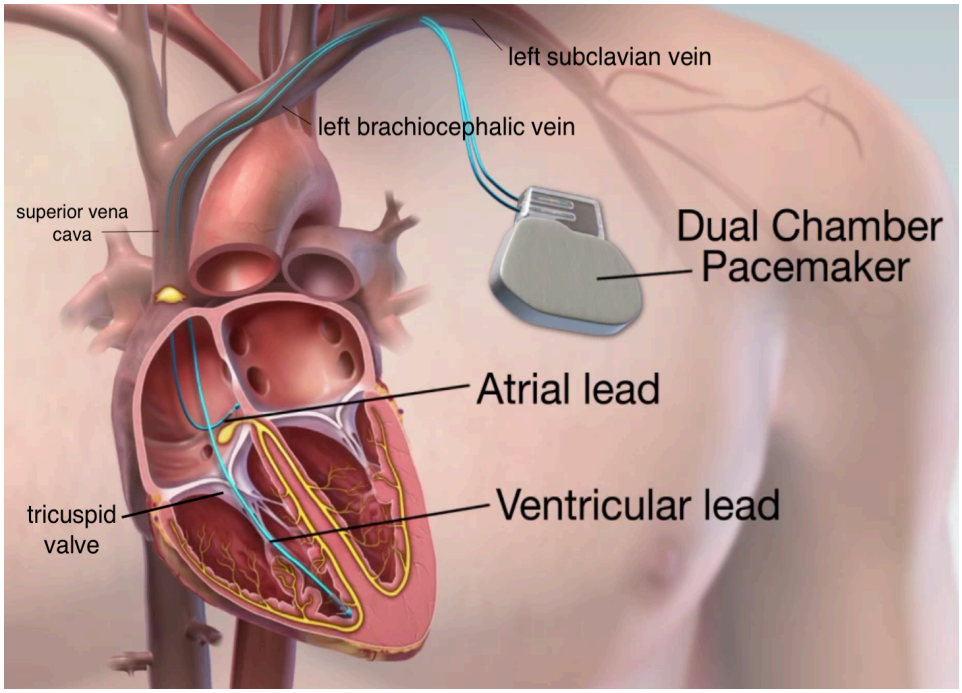


Image 2: An implanted dual chamber pacemaker. Two separate electrodes and leads are depicted: one in the RA, the other in the RV. The image is from the Australian One Heart Website[17].

The electrodes register the heart's electrical activity and pass on this information to the generator, where it is computed and the according electrical response is sent back via the leads to

the electrodes. Depending on the settings of the PM, a device can either register bradycardia, tachycardia or a normal heart beat and in response either stimulate or suppress depolarization within the heart muscle tissue[23].

General surgical complications after a PM implantation include "wound infection, bleeding, thrombosis, pulmonary artery embolism, nerve damage or tissue damage due to poor positioning during the intervention"[24]. Furthermore, specific complications include possible damage from puncturing such as pneumothorax, hemothorax, heart perforation with pericardial effusion and tamponade, air embolism, or other accidental perforation of blood vessels.[25] The leads themselves can also lead to complications, such as irritation in the myocardium paradoxically inducing arrhythmia, or can dislocate after the procedure possibly damaging surrounding tissue[24]. However, the overall risk of a PM implantation is low nowadays and can be performed rather securely[24].

There is the universal NBG code used for describing PMs technically consisting of up to five letters. It was created together by the North American Society of Pacing and Electrophysiology (NASPE) and British Pacing and Electrophysiology Group (BPEG)[26,27]. The table below cited from Bernstein et. al.[27] summarizes what each of the five letter positions symbolize.

Table 1: NBG Pacemaker Code[27]

Position	I	II	III	IV	V
Category	**Chamber(s) Paced**	**Chamber(s) Sensed**	**Response to Sensing**	**Rate Modulation**	**Multisite Pacing**
Letter and Meaning	0 = None A = Atrium V = Ventricle D = Dual (A+V) S= Single (A or V)	0 = None A = Atrium V = Ventricle D = Dual (A+V) S= Single (A or V)	0 = None T = Triggerred I = Inhibited D = dual (T+I)	0 = None R = Rate Modulation	0 = None A = Atrium V = Ventricle D = Dual (A+V)

Table 1 lists and explains the different possibilities for the five letter NBG code used to define PM design and settings.

The first position describes in which chamber the electrodes register the heart's activity and the second position describes in which chamber the electrodes send signals to. The third position describes how or when the PM sends signals. Triggered means the device will only stimulate if intrinsic activity is sensed. If, for instance, there is impaired conduction in the AV-Node, the device can stimulate the ventricle if activity is registered in the atrium and permit an endogenous

heart rate. Inhibited means that the device only sends impulses if no intrinsic activity is sensed. For example, if the Sinus node does not stimulate enough on its own, the PM can do so until it does, but no atrial to ventricular coordination is given. The fourth positions describes as to whether the device can adapt the stimulated heart rate according to the patients bodily functions such as exercise or sleep. The fifth position describes if the device stimulates in more than one area within a chamber, however this letter is used less than the others[26,27].

1. 2. 3. 2. Implanted Cardioverter Defibrillator

An implantable cardioverter defibrillator (ICD) detects ECG irregularities such as VT and in response is able to defibrillate the heart with its electrodes. An ICD is usually combined with a PM, but does not have to be[28]. An ICD must have a minimum of one electrode in the RV in order to correctly sense an arrhythmia and apply an electrical shock, using the generator as an antipole to the electrode[29].

1. 2. 3. 3 Cardiac Resynchronization Therapy

A cardiac resynchronization therapy (CRT) device allows atrium-synchronized biventricular pacing. A CRT typically has one sensing electrode in the RA and two pacing electrodes, one right ventricular and the other left ventricular externally along the coronary sinus[30]. It paces according to atrial impulse generation and secures a more simultaneous, coordinated contraction of the ventricles, hereby improving the heart's overall pump function[29,31].

1. 2. 4. Indications for Cardiac Pacing

1. 2. 4. 1. Indications for Pacemaker

One group of patients for whom a PM is relevant for are patients with bradycardia. Symptomatic persistent SSS and symptomatic intermittent SSS are both indications for a PM implantation, mostly two chambered[32,33]. An intrinsic persistent or intermittent AV-Block second or third degree, regardless of whether they are symptomatic or not, are also indications for a PM, mostly two chambered as well[32-34]. A bundle branch block with a positive electrical physiological examination or an alternating bundle branch block, regardless of whether it is symptomatic or not, are further indications for a PM implantation[32,33]. The presence of an AV-Block and persistent VF are also indications for a PM, however rather one chambered in the RV[32]. Patients with Carotid Sinus Syndrome is an indication for a PM as well[32,33]. This, when pressure applied

to the carotid arteries, causes a symptomatic decline in heart rate, including everyday activities such as turning one's head[35].

There are some constellations in which the implantation of a PM is not primarily indicated but should be considered based upon other factors such as older age, risk of falling with injuries or accompanying illnesses, especially cardiac. These include AV-Block second degree Type I located either infra- or intra-hisian, asymptomatic Sinus pauses or syncopes without diagnostic findings[32,33]. In these cases, the implantation of a PM has to be carefully considered by a physician based upon the individual situation of the patient. If a patient develops a relevant and persistent arrhythmia such as AV-Block after a myocardial infarction or cardiac surgery, then a PM can be necessary[32,33].

All reversible bradycardia, due to intoxications for instance, are not an indication for a PM implantation[32,33]. A documented but not symptomatic bradycardia is not an indication as well[32]. A physiological bradycardia, such as in athletes, is not an indication for a PM either[32]. Lastly, an asymptomatic single bundle block is also not primarily an indication[32].

In Germany in the year 2015, SSS was the most common indication making up 36,6% of all indications for newly implanted devices[36]. Second was third degree AV-Block with 29,3 %, however when including first and second degree diagnoses, AV-Block over-all was the most common reason for a new PM making up almost half of the indications, namely 43,3%[36]. Three fourths of devices were set in D-D-D, followed be V-V-I and only a minute portion of patients received a CRT[36]. Amongst all newly implanted PMs, 42,4% of the patients were over 8.0 years old[36]

1. 2. 4. 2. Indications for an Implantable Cardioverter Defibrillator

An ICD can be implanted for primary or secondary prophylactic reasons. Concerning primary prophylaxis, indications for an ICD implantation encompass mostly hereditary diseases regarding arrhythmias and myopathies such as Brugada Syndrome, Long-QT syndrome and genetic disorders with an increased risk of sudden cardiac death such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy[37].

An ICD can be considered for primary prophylaxis for patients who have a secondary high risk of arrhythmia, for example for patients with cardiomyopathy, whose LVEF remains lower than 35%, with or without symptomatic ventricular extrasystoles or non-persistent VT[37].

The indication for a secondary prophylactic ICD is essentially based upon the presence or occurrence of hemodynamic unstable ventricular tachycardic conditions. An ICD is primarily indicated when VF or generally VT induce cardiac arrest, syncopes or cardiac shock or no specific cause is found for such conditions[37]. If a syncope was not documented in an ECG, but a patient's LVEF is ≤ 40 % and VT is inducible, then an ICD is indicated as well[37]. Another indication for a single chamber ICD is HF with a NYHA classification of II-III where LVEF is ≤ 45%[37]. Furthermore, patients who have suffered myocardial infarction longer than four weeks ago and have a LVEF of ≤ 30% also qualify for an ICD[37].

1. 2. 4. 3. Indication for Cardiac Resynchronization Therapy

The indication for a CRT largely depends on the QRS complex in the ECG, left ventricular ejection fraction (LVEF) and accompanying arrhythmias. If a left bundle block is present, LVEF is less than 35%, New York Heart Association (NYHA) classification is II, III, IV and the QRS complex is greater than 120ms, the implantation of a CRT is indicated, almost always biventricular[32,33]. Over all, clinical practice shows that female patients with a broadened QRS complex, left bundle block and non-ischemic cardiomyopathy respond best to CRT[32]. In Germany in 2011, roughly 5-10% of patients with HF had a clinical indication for a CRT[32].

A CRT implantation should or can be considered but is not primarily indicated if the bundle block is not left, the LVEF is less than 35%, the NHYA classification is II-IV and the QRS complex is greater than 120ms[32,33]. The same situation applies to patients with persistent VF, low LVEF and a broadened QRS complex[32].

An isolated LVEF below 35% with a QRS complex less than 120ms is not an indication for a CRT[32].

If an ICD therapy is planned, then a CRT-D device should be implanted[32,33]. However, if a patient has a life expectancy of under one year due to severely advanced HF, severe kidney failure or dialysis, cachexia, fragility or other severe accompanying illness a CRT-P should be considered instead due to less expected complications after its implantation[32,33].

1. 3. The Tricuspid Valve

1. 3. 1. Anatomy and Function of the Tricuspid Valve

Image 3 below depicts the anatomy of the TV.

Image 3: Anatomy of the Tricuspid Valve[1]

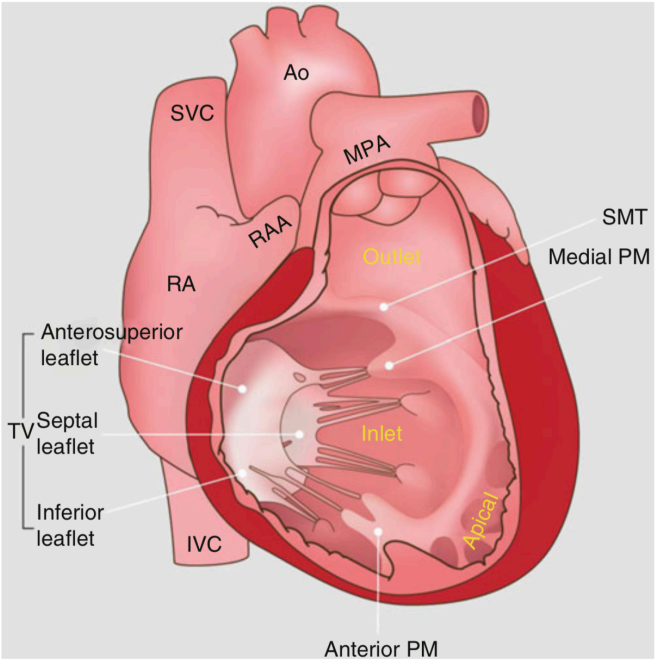


Image 3: Anatomy of the right and left heart, showing the exact location of the TV, the chordae tendinae and papillary muscles. The image is from Mazur et al.'s book "CT Atlas of Adult Congenital Heart Disease"[36]. Ao: aorta, IVC: inferior vena cava, MPA: main pulmonary artery, PM: papillary muscle, PV: pulmonary valve, RA: right atrium, RAA: right atrial appendage, SMT: septomarginal trabeculations, SVC: superior vena cava, TV: tricuspid valve.

The TV is located between the RA and RV, thus its latin name "valva atrioventricularis dextra"[38] (Image 3). There are three leaflets, namely cuspis anterior, posterior and septalis, consisting of a thin avascular connective tissue, covered with endocardium[38]. The leaflets are joined onto a ring-like base, or annulus, and strung by the chordae tendinae onto the papillary muscles which connect the leaflets to the RV wall, enabling the valve to close[38]. The TV's role is to prevent blood streaming back from the RV into the RA during a systole, while the RV contracts and the pressure in the RV exceeds the pressure in the RA[38].

1. 3. 2. Pathophysiology of the Tricuspid Valve

Valvular heart diseases (VHDs) are the most common cardiovascular diseases following arterial hypertension and coronary heart disease[39-41]. Principally VHDs are etiologically divided into congenital and acquired diseases, the latter encompassing degenerative processes, infections or rheumatic events. Furthermore, VHDs are classified as valvular stenoses, a narrowing of the valve's diameter, or valvular insufficiencies, also known as regurgitation. This means that the valve does not close completely and blood can flow retrograde[42,43]. The most common VHD in

Germany is aortic valve stenosis, which accounts for 43% of all VHDs[42], followed by mitral valve insufficiency with 10-15%[43], of which the majority of both are acquired diseases[43].

Diseases of the TV occur less making up approximately 4-5% of the acquired valve defects[44]. Tricuspid Regurgitation (TR) however is more common than tricuspid stenosis, which is almost exclusively a complication of rheumatic fever[45]. TR is often accompanied by other VHD of the left heart[46].

Acquired TR is much more frequent than congenital TR. Acquired TR can be caused by direct lesions to the TV, a so-called "organic" origin, including bacterial infections, carcinoid syndrome, trauma or rheumatic fever[45]. Much more common however, is TR caused by a secondary dilation of the annulus, a so-called "functional" origin[45]. In most cases, it is caused by pre-existing diseases of the left heart or pulmonary circulation, which increase the overall pressure in the right heart. Examples are pulmonary arterial hypertension (PAH), pulmonary or pulmonary valve stenosis, RV myocardial infarction, RV cardiomyopathy or left heart failure (LHF)[18,45,47-49].

In TR, blood flows from the right ventricle back into the right atrium during systole, due to the lack of sealing by the pathologically altered TV. Incipiently, this can remain without major hemodynamic effects, or rather can be tolerated for a period of time depending on the general condition of the heart[47]. The aftermath of the backflow of blood into the RA depends on the duration and the actual volume of the blood flowing back. Over time, a greater diastolic pressure is needed in the RA to push the additional blood back from the RV at atrial level, which can lead to RA hypertrophy. If, regardless of the etiology, the mean pressure in the pulmonary circulation is increased, the afterload of the RV increases and there must be an increase in pressure in the systole as well in order to eject the blood. This in can additionally lead to right ventricular hypertrophy. In the long run, this can lead to cardiac insufficiency. In the worst case, because the effective cardiac output is decreased, this can induce acute right heart decompensation in the event of sudden pressure increases, such as pulmonary artery embolism, or increased physical activity[44,46,47].

Harrison's Principle of Medicine states that "the tricuspid valve is the most underestimated HVD" and that " roughly 35% of patients with severe TR die within the next 12 months" after diagnosis[46].

1. 4. How to diagnose Tricuspid Regurgitation

1. 4. 1. Clinical Symptoms

The clinical symptoms of TR are mostly contingent on the presence and extent of accompanying right heart failure (RHF) or even LHF, as TR is often not the singularly diagnosed VHD. The symptoms of RHF include fatigue, exertional dyspnoea according to the NYHA criteria[50], weight gain and peripheral oedemas, feeling of fullness or bloatedness, lack of appetite and a distended abdomen, a visible jugular vein congestion hepatomegaly with systolic pulsations, ascites, and reflux. TR is symptomatic in auscultation as a holosystolic, highfrequent sound in the fourth or fifth intercostal space left parasternal or in the xiphoid region. This sound is intensified during inspiration, which is called the "Carvallo's Sign"[46]. A third heart tone can appear as well. This breathing dependency is pivotal, as the auscultation symptoms can otherwise easily be confused with mitral regurgitation[18,46,51].

1. 4. 2. Tricuspid Regurgitation Classification and Echocardiology

TR can also be diagnosed with medical imaging techniques. A chest x-ray might reveal indirect signs such as an enlarged heart. Nevertheless, echocardiography is the standard procedure of documenting TR. Table 2 summarizes qualitative, semi-quantitative and quantitative methods of recording TR[51].

Table 2: Echocardiographic Values for Observing Tricuspid Regurgitation[52-54]

Methods		Mild TR	Moderate TR	Severe TR
Qualitive	Intensity of Insufficiency Jet in RA	dense/triangular, early peaking ⟶ +		
	Valve Morphology	abnormal/flailing leaflets ⟶ +		
	Volume of Systolic Insufficiency Jet into RA	< 1/3	1/3- 2/3	> 2/3
Semi-Quantitative	Vena Contracta Width (mm)	< 6	≥ 7	≥ 7
	PISA Radius (cm)	< 9	< 9	≥ 9
	Systolic Reverse Hepatic Vein Flow	/	++	+++
Quantitative	EROA (cm^2)	< 40	< 40	≥ 40
	R Vol (ml/beat)	< 45	< 45	≥ 45
	RA and RV Enlargement	-	-/+	++
Other	CVP mmHg	/	+	++
	TAPSE mm	< 20 sign of reduced right heart function		

	TR Vmax (m/s^2)	≥ 2.8 is considered pathological

Table 2: Overview of echocardiographic values used for describing TR[53,54]. PISA: Proximal Isovelocity hemispheric Surface Area; EROA: Effective Regurgitant Orrifice Area; R Vol: Regurgitant Volume, TAPSE: Tricuspid Annular Plane Systolic Excursion; CVP: Central Venous Pressure; TR Vmax: TR maximum Jet Velocity; mmHG: millimeters of mercury.

One approach to assess TR is the optical observation of the systolic insufficiency jet itself which is the blood that streams into the RA in the case of TR. The denser the signal and the more area it seems to take up in the RA in a colored-doppler sonography, the worse TR can be expected. Early peaking refers to the resulting parabel shape of the velocity curve, in which the velocity decreases in the late systolic period quicker than usual. Additionally, one can examine the TV itself and try to identify a morphological abnormality. Vena contracta refers to the smallest diameter at the narrowest part of the insufficiency jet underneath the opening of the respective valve. The wider it is, the worse TR can be estimated. The PISA radius is used to estimate the surface area of the valve opening, through which the blood of the regurgitation jet flows. This is also known as EROA. An increase in both implies that more blood flows retrograde through the TV. Furthermore, reverse hepatic vein flow, which does not occur physiologically, is a sign of reduced right heart function. RA and RV enlargement and an increased CVP are possible consequences of TR. The greater the dilation and CVP, the more likely TR is severe. TAPSE is also a value that is used to asses overall right heart function, which can be reduced if TR is severe. Lastly, TR Vmax is used to estimate the right heart's maximum pressure, which is increased in advanced TR. It can also be used to estimate whether a patient has PAH, which is sometimes diagnosed parallel to TR and can worsen it[54-58].

It is important to note that all of these values must be interpreted collectively. The echocardiographic values can be pathological independently from one another, without making the occurrence of another value obligate. They must also be considered in contextually to the clinical symptoms reported by a patient. Lastly, the more advanced the TR is, the easier it is to measure these values. If the TR is incipient, some of these values can lie within normal range or be ambiguous[18,56,59].

1. 5. Aim of the study

Germany has one of the highest new implantation and exchange rates of PMs in Europe. In 2011, about 1291 PM implantations and exchanges per million population occurred in Germany, which was even higher than that of the European average of 938 per million population[32]. The number

of new implantations has since decreased minimally, however the number of PM unit exchanges has risen[36]. Yet all together, the number of PM operations remains high in comparison. In 2015 in Germany for example, it totaled to 75,730 operations[36]. That same year, Germany still had the highest number of new implantations per million population with 922 operations compared to Denmark, Switzerland and Sweden[36].

Commonly described complications after PM implantations pertain primarily to surgical aftermath. There are some complications though that have not been scientifically secured. In the case of a PM including a RV lead, the lead not only passes through, but remains lying in the tricuspid valve after implantation. Some authors suspect that this could lead to TR as a long-term complication after implantation[46,60-63]. As specified above, TR alone can induce severe medical consequences. If this phenomenon after PM implantation is veracious, it can have a far-reaching effect, especially considering the high number of interventions.

Findings in literature regarding this suspicion are nevertheless heterogenous and inconstant. The aim of this study is to examine the possible correlation between PM implantation and TR in accordance with reliable scientific standard and quality.

1. 5. 1. Research Questions

The aim of this study is to investigate the following research questions:

- Does the implantation of a cardiac rhythm device influence the TV function, and can it induce TR?
- Which parameters regarding the TV does the implantation of a cardiac device affect?
- Does the implantation of a cardiac device impact probability of survival?

Methods

2. 1. General Study Design

The study was conducted retrospectively at the Charité Universitätsmedizin Berlin, Germany in 2016 until 2018. The study compared data between a PM group and a control group. Two-dimensional transthoracic echocardiographic follow-ups at different time intervals, focused on the evaluation of the tricuspid valve function, as well as baseline characteristics were examined for both groups. Furthermore, it was recorded whether patients in both groups were still alive or deceased.

2. 2. Ethics Votum

The Study was approved by the Ethics Committee of the Charité Universitätsmedizin Berlin, Germany (Order Number: EA1/394/16).

2.3. Study Population

2. 3. 1. PM Group

First, a pool of patients eligible for the study for the PM group were recruited. This consisted of all patients who had received one of the following four implantable cardiac rhythm devices at the Charité Universitätsmedizin Berlin between 2010 to including 2016: PM (PM), implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT) or cardiac contractility modulation (CCM). .

The patients had to have had at least one echocardiography performed at the Charité Berlin, Campus Benjamin Franklin during the same time period. Both men and women from the age of 18 years onwards were included. The patients' initial indications for the implantation of the devices were not regarded**.** The number of devices implanted per patient and the individual frequency settings of the devices were also not regarded.

In a second step, patients were removed from the original pool if the following criteria did not apply:

- Each patient had to have at least one two-dimensional transthoracic echocardiography (TTE) before and after the implantation of a cardiac device.

- The TTEs before and after the implantation had to include an examination of the tricuspid valve.
- Each TTE had to be fully documented, including the images that were made during the examination.
- The implanted devices were not limited in lead number as long as at least one lead passed through the tricuspid valve.
- A patient did not undergo catheter ablation

In a final step, the remaining patients were divided into groups depending on when their follow-up TTE examinations had been performed. Patients was assigned to one of the three groups: follow-up within 30 days after implantation, follow-up within 12 months after the implantation and follow-up at least one year after the implantation.

2. 3. 2. Control Group

Based on the characteristics of the final PM group, a pool of patients eligible for the study for the control group were recruited. This consisted of all patients, who had received at least two echocardiographies at the Charité Universitätsmedizin Berlin, Campus Benjamin Franklin between 2010 to including 2016. Both men and women from 29 to 93 years of age were included. The patients were not allowed to have any cardiac device implanted or have undergone catheter ablation within their entire lifespan.

In this original pool of patients, it was not technically possible to have the gender of the patients automatically listed. The gender male or female was assigned manually to each individual patient. All patients whose gender could not be clearly assigned were removed from the original pool.

In a third step, all patients who received less than four echocardiographic examinations were removed from the original pool. Here could not yet be differentiated whether the examination was a TTE or a transesophageal echocardiography (TEE).

The remaining patients in the control group were then matched with the patients in the PM group based on their gender and age. If an exact match in age was not possible, an age difference of +/- one year was accepted. For each patient in the PM group, up to four controls were assigned.

The remaining matches were then re-evaluated. The final patients for the control group were chosen manually based upon mutual baseline characteristics to the PM group. Final patients for the control group were chosen if the following criteria applied:

- The control had the same Body Mass Index (BMI) classification as the exposed

  and

- The control had the same amount of diagnosed accompanying illnesses

Controls who had the same or similar diagnosed accompanying illnesses were preferred. If a control had the identical diagnosed accompanying illnesses, but did not have the same BMI classification, the patient was included in the control group if the BMI did not differ from the PM's by more than 5kg/m^2.

If no control could be matched to a patient in the PM group, this patient was excluded from the PM group.

Finally, the patients in the control group were assigned to the same follow-up groups concerning their echocardiographic examinations as the PM group.

2. 4. Baseline Characteristics

The following baseline characteristics were recorded for both the PM and the control group:

- whether any other cardiovascular operation had been performed, such as a bypass or valve replacement

- whether the patients had been diagnosed with coronary heart disease, renal insufficiency, peripheral artery disease, arterial hypertension, diabetes Type I or II, pulmonary embolism or stroke

- BMI in kg/m^2

The BMI was classified into the four following groups based on the recommendations of the World Health Organization (WHO)[64]:

Table 3: BMI Classification according to the WHO[63]

BMI in kg/m^2	Classification	Assigned Numeral
<18,5	underweight	I
18,5-24,9	normal weight	II
≥25,0	overweight	III
≥30,0	obese	IV

Table 3 lists the BMI classifications used in clinical practice.

For every patient in the PM group, the type of cardiac device as well as how many chambers and leads they had were recorded.

2. 5. TTE Evaluation

The procedure of evaluating the TTEs was the same for both the patients in the PM, as well as the control group. The TTEs were two-dimensional, performed by experienced examiners in the Charité Universitätsmedizin Berlin between 2010 until 2016 using a Vivid E9 Ultrasound System, manufactured by GE Healthcare.

Each Patient had an initial TTE. In the PM group, this was the TTE before a cardiac rhythm device was implanted. In the control group, it was the patient's chronologically first TTE. For each patient a total of maximum three TTE follow-ups were evaluated, depending on whether a TTE had been performed within one month, within 12 months or after a minimum of one year after the initial examination. If a patient had more than one TTE within one time-frame, the chronologically latest examination was included. The patients did not have to have a TTE for each time-frame.

For each TTE evaluation, echocardiographic images and written reports were included. The diagnosed Tricuspid Regurgitation (TR) Grading and other measurements were recorded from written reports. The maximum tricuspid regurgitation velocity in m/sec (TR Vmax), vena contracta width in mm, RA volume and the PISA in ml were derived manually from the echocardiographic images.

2. 5. 1. Written Reports

For each examination, the exact TR Grading diagnosed by the examiner was recorded, whether it was documented as a roman numeral or written out. Examiners recorded the TR Grade singular or as a combination of two Grades. In clinical practice, TR severity is divided into four

classifications, namely 0, I, II and III with III being most severe. This study classified the TR in half steps allowing seven possible classifications, shown in Table 4.

Table 4: TR Classification used in this Study

TR Grade Roman Numeral (diagnosed by Examiner)	TR Grade written out (diagnosed by examiner)	Recorded TR Classification
0	none	0
0-I	trace	0,5
I	mild	1,0
I-II	mild to moderate	1,5
II	moderate	2,0
II-III	moderate to severe	2,5
III	severe	3,0

Table 4 describes how the TR gradings in written reports evaluated in this study were documented. The documentation allowed TR to be categorized precisely into half steps.

Additionally, the following results were recorded from the written reports:

- tricuspid annular plane systolic excursion (TAPSE) in mm
- left ventricular ejection fraction (LVEF) in %
- pulmonary arterial pressure (PAP) in mmHg
- central venous pressure (CVP) in mmHg

If no CVP had been documented, a CVP of 5mmHg was assumed[56,65].

2. 5. 2. TTE Images

The TR Vmax was measured manually using the images made during an echocardiography by the examiner, shown below in image 4.

Image 4 Measurement of the TR Vmax (original image from study)

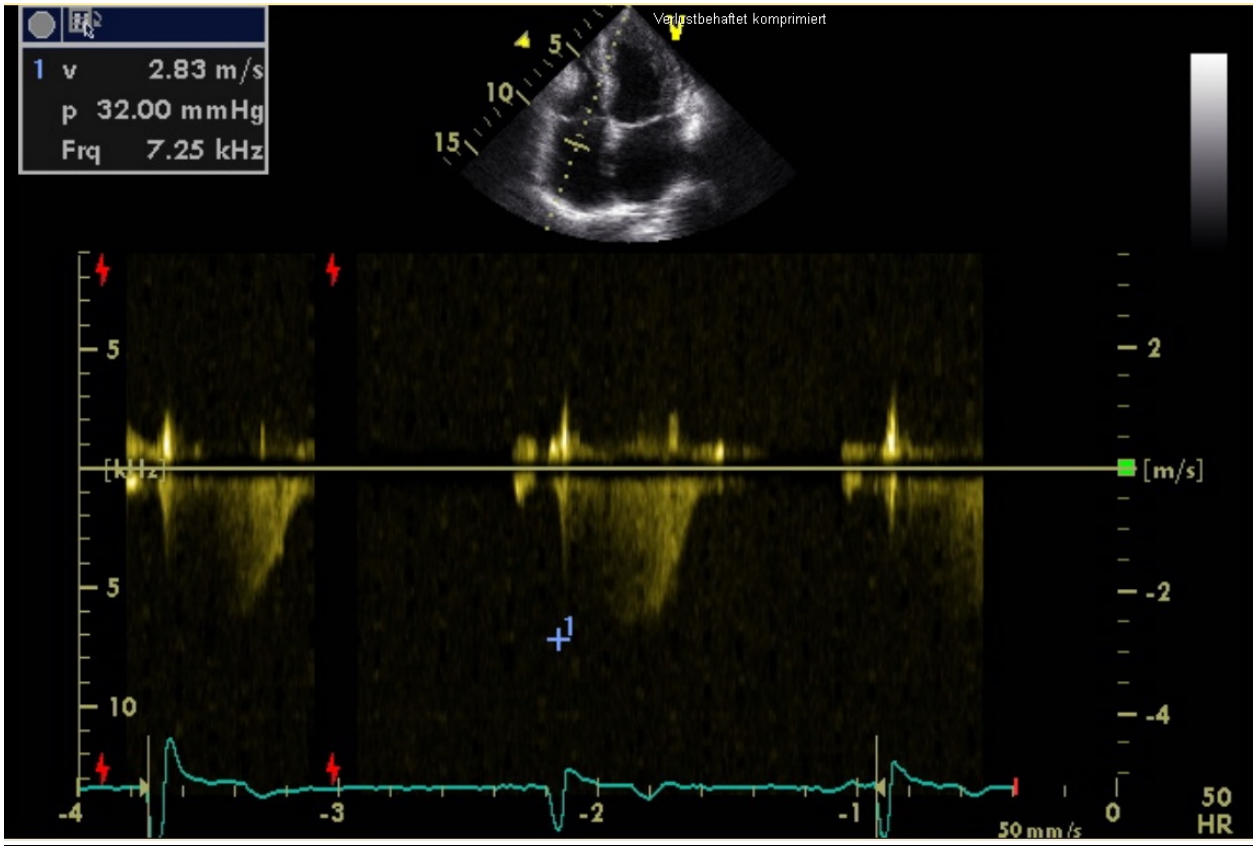


Image 4: original echocardiographic image made in this study demonstrating how the TR Vmax was determined.

The images used for measurements were accessed retrospectively. They were apical four chamber views with a continuous wave doppler focused on the tricuspid valve. As shown in Image X, the tricuspid valve's regurgitation velocity was then displayed. In this study, the velocity in m/s was measured manually using a measuring tool available in Centricity CARDDAS Xi[2] Program. A line was drawn from the zero line (x axis) to the maximum point on the curve (y axis).

Furthermore, the following three values were derived manually from echocardiographic images as well:

- The width of the vena contracta in mm
- PISA in mm
- RA Volume in ml end-diastolic

2. 5. 3. Calculated Data

The systolic pulmonary Artery Pressure (SPAP) was calculated additionally to the recorded PAP based on the modified Bernoulli Equation[66]:

$$\mathbf{P_{PA\text{-}Syst} = 4 \times (TR\ V_{max})^2 + CVP}$$

where:

$P_{PA\text{-}Syst:}$ systolic pulmonary Artery Pressure in mmHg

TR $V_{max:}$ maximum tricuspid regurgitation velocity in m/sec; here used as the pressure gradient between the RV and RA[67]

CVP: central venous pressure in mmHg

2. 6. 1. Enquiry

On the 24th of April 2018, an enquiry was made at the Landesamt für Bürger- und Ordnungsangelegenheiten Berlin, Germany (State Office for Residents' and Regulatory Affairs). This enquiry was a request on information as to whether all patients in this study were registered as alive or deceased. A request only applied if patients were registered in Berlin, Germany. For each request, the name and date of birth for each person was stated. The enquiry was made via iDGARD System, an official electronic document management system that allowed a secure and protected upload, provided by the Landesamt für Bürger- und Ordnungsangelegenheiten Berlin, Germany.

2. 6. 1. Granted Enquiry

The enquiry was granted on the 25th of April 2018. Information as to whether a patient was registered as alive or deceased was provided for each patient. If a patient was deceased, the date of death was stated. No information could be provided if one of the following three situations occurred: a patient was not registered in Berlin, Germany; there was more than one person with the same name and date of birth; there was a ban on disclosure for a patient, due to legal reasons for example. It was not specifically named, which situation applied if no information was provided for a patient.

2. 7. Data Acquisition and Presentation

Data was recorded retrospectively and obtained through medical reports and patient records in the Charité SAP Software System. Additional echocardiographic information was obtained through the Centricity CARDDAS Xi^2 Program. The collected data was documented in tables in Microsoft Excel Version 15.27 and SPSS Version 24.0 (German Language). All graphics and charts were created using both of these programs.

When data gathering was completed, the patients included were anonymized and checked for duplicates.

2. 8. Statistics

All statistical tests were performed using SPSS Version 24.0 and Stata Software 15. The statistical procedures were consulted by and conducted with the help of the Institute of medical Biometrics und clinical Epidemiology of the Charité Berlin. All graphs were created with SPSS Version 24.0 and Microsoft Excel Version 15.41.

2. 8. 1. Descriptive Statistics

All variables were tested for normal distribution graphically by evaluating each individual variable's histogram, specifically by assessing their skewness. For all nominal variables, absolute and relative frequencies were shown. Ordinal scaled variables were characterized by their median and interquartile range (IQR). Interval scaled variables were characterized by their mean and standard deviation (SD).

2. 8. 2. Statistical Tests

The baseline characteristics were analyzed and the p-values were calculated from either a linear mixed model (random intercept model) or a binary mixed model (random intercept model) using SPSS 24.0 or STATA 15.

For the following tests (Wilcoxon Signed-Rank, mixed linear model; described below), the control group's results were only included, if the matched patient in the PM group had corresponding data for the equivalent follow-up.

The median values for TR, mean TR Vmax, TAPSE and LVEF for all follow-up periods for both groups were compared using the Wilcoxon Signed-Rank Test on SPSS Version 24.0. The

following assumptions were met: the independent variable was paired and the dependent variable was at least ordinal scaled, it was only approximately normally distributed but it had an approximately symmetrical distribution of differences[68,69]. A significance level was set at $p<0.05$. Each follow-up period was compared to the initial TTE separately.

The observed echocardiographic data was analyzed using a mixed linear model for paired variables on SPSS Version 24.0. This test was used to compare the observations explicitly between the PM and control group. It was assumed that all variables were normally or approximately normally distributed. Time was not set as continuous. A significance level of $p<0.05$ was chosen. The three levels applied were: the match identification (a paired PM and control patient shared one match identification), the patient's individual identification (every patient included in this study received their own individual identification) and the recorded variable being compared. The medians and means of each characteristic for each follow-up period were compared between the PM and the control group in order to assume whether differences were statistically significant.

The Kaplan-Meier survival curve was created using SPSS Version 24.0. The beginning date of the observation period was the first echocardiographic examination performed amongst all patients included in this study, namely the 6th of September 2010. The ending date of the observation period was the last time data was observed and recorded for all patients in this study, namely the date on which the enquiry was granted, the 25th of April 2018. The Kaplan-Meier survival analysis was also performed using SPSS Version 24.0 in order to establish whether a difference in survival probabilities was significant. Here, three tests were applied: Log-Rank Test (Mantel Cox), Breslow (generalized Wilcoxon) and Tarone-Ware. The null hypothesis was that there was no difference in survival probabilities between the PM and control group. Results were significant if $p<0.05$. The occurring event was death. Censored patients were patients, who had been removed from the study over time or to whom the occurring event did not happen to, but it was assumed it would after the observation period had finished. Only patients to whom information was provided for as to whether they were registered as alive or deceased were included.

Results

3. 1. Study Population

3. 1. 1. Selection of Patients for the PM Group

The selection process of patients for the PM group is shown below in figure 1.

Figure 1: Selection of Patients for the PM Group

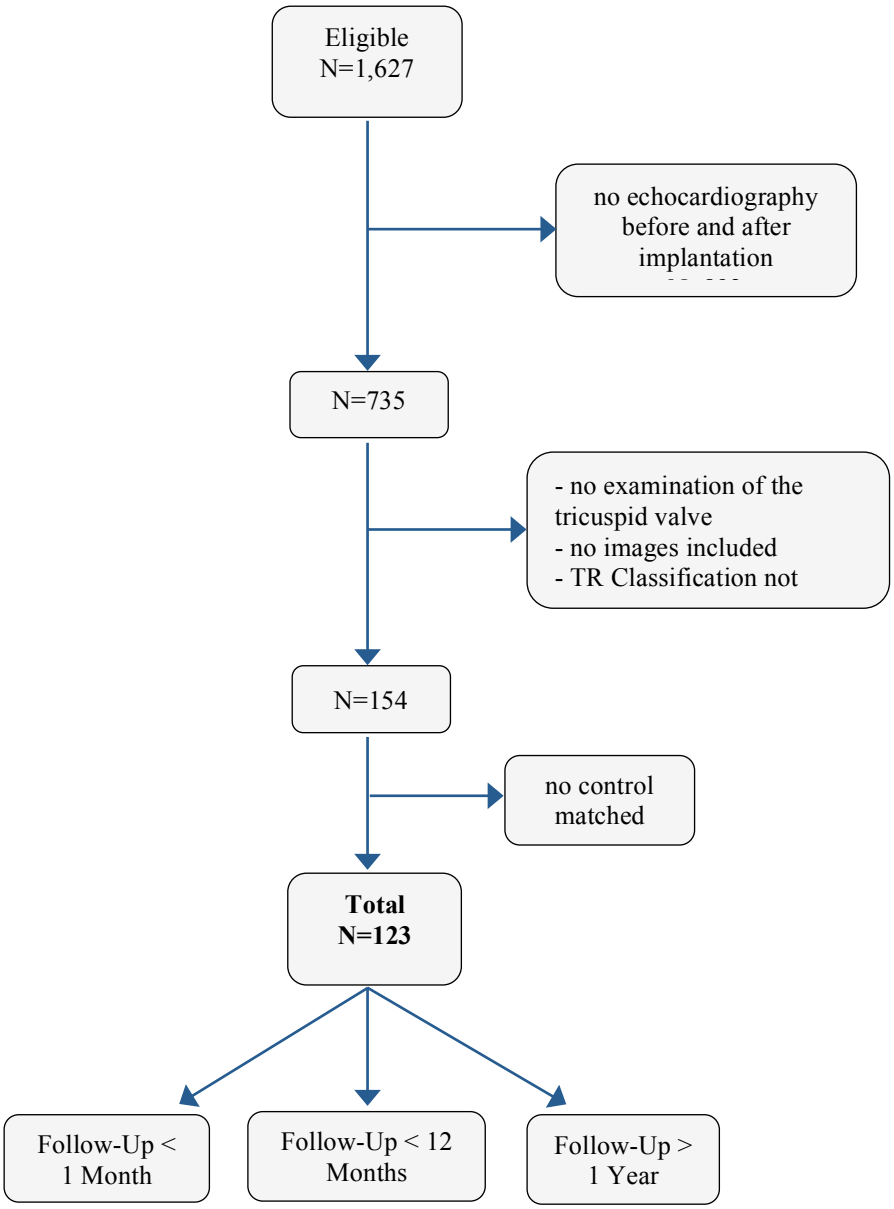


Figure 1 shows the selection process of patients allocated to the PM group.

A group of 1,627 patients eligible for the study were recruited. Three steps were taken in order to include and exclude patients from the study. First, 892 patients were removed because they did not have an echocardiography available before and after an implantation of a cardiac device. Second, 581 patients were removed because their echocardiographies did not meet the criteria set for inclusion. Lastly, 31 patients to whom no control could be matched to were excluded.

The PM group consisted of a total of 123 patients. 42 patients (34%) had received a follow-up TTE within one month after implantation, 47 patients (38%) within 12 months and 103 patients (84%) at least one year after implantation.

Table 5: Specific Characteristics for the PM Group

Specific Characteristics for the PM Group	
Total Number of Patients with PM included N (%)	123 (100%)
Mean Age at Implantation of Cardiac Device in Years	70 ± 12.5
Devices N (%):	
PM	60 (49%)
ICD	46 (37%)
CRT	17 (14%)
CCM	0
Mean Number of Implantations	1
Mean Number of Leads per Device	2
Mean Number of Leads passing Tricuspid Valve	1

Table 5 lists the specific data only pertaining to the PM group, such as types of implanted devices, and how many leads they had.

As shown in Table 5, the mean age of patients at implantation was 70 years, with a standard deviation of 12.5 years. About half of the patients totaling 49% (n=61) had a PM, 37% (n=46) had an ICD and further 14% (n=17) had received a CRT. The mean number of implantations per patient was one device. The mean number of leads per device per patient was two leads. The mean number of leads passing through the tricuspid valve was one lead.

3. 1. 2. Selection of Patients for the Control Group

The selection process of patients for the control group is shown below in figure 2.

Figure 2: Selection of patients for the control group

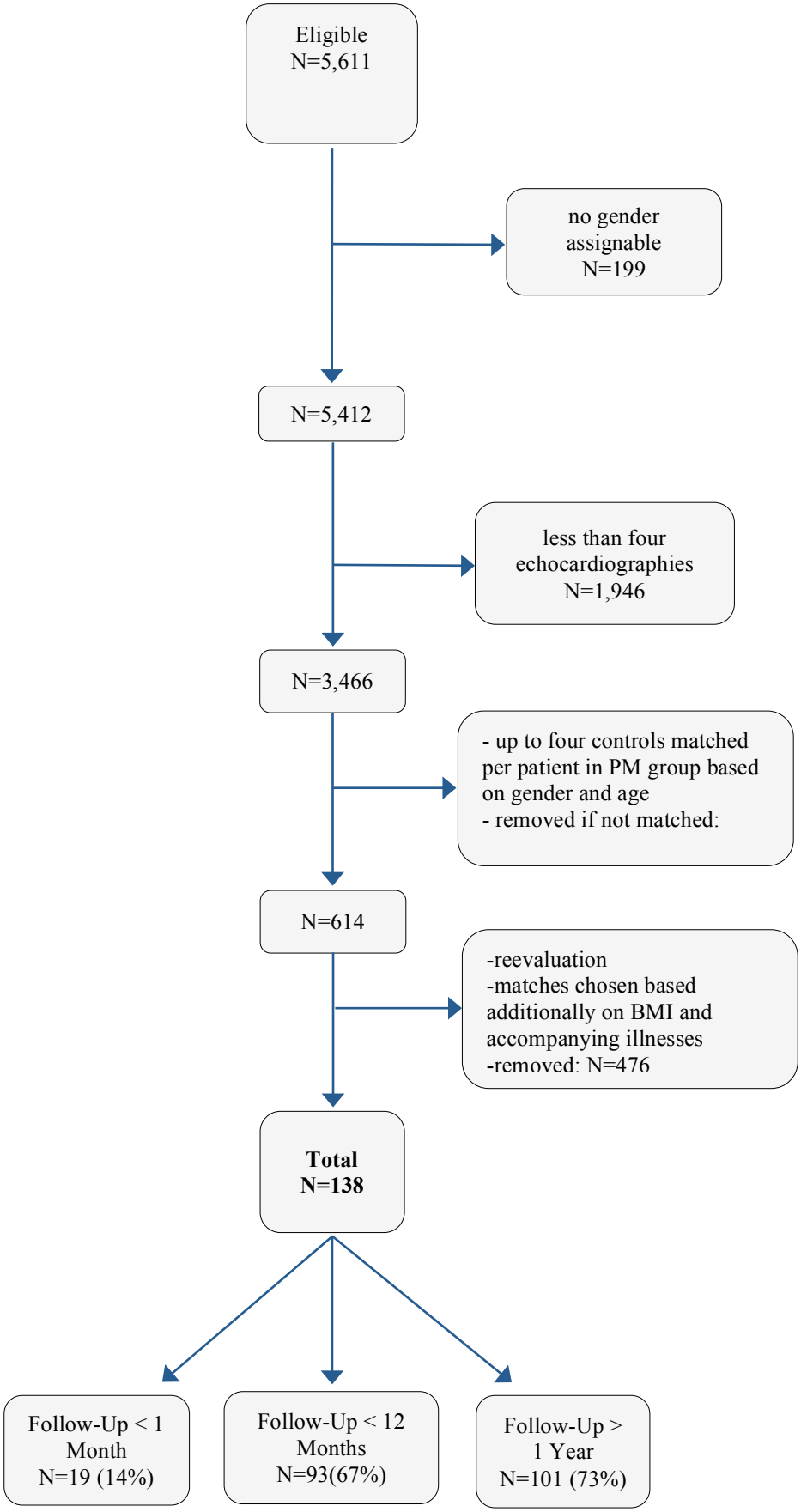


Figure 2 shows the selection process of the patients allocated to the control group.

A group of 5,611 patients eligible for the study were recruited. 199 Patients to whom no gender could be assigned to were removed first. Next, 1,946 patients were excluded because they had a total of less than four echocardiographies available. In the third step, the remaining patients were matched to a patient in the PM group based on gender and age, where a maximum of four controls could be matched to one patient with implantation. 2,852 patients were not matched and consecutively removed. The matches were then reevaluated and finally chosen based additionally on BMI and their accompanying illnesses. 476 were excluded.

A total of 138 patients were included in the control group. 19 patients (14%) had received a follow-up TTE within one month after their first echocardiography, 93 patients (67%) within 12 months and 101 patients (73%) had received a follow-up at least one year afterwards.

3. 1. 3. Baseline Characteristics

The baseline characteristics and demographics of the study population are summarized below in table 6. The mean age of patients in the PM group was 75 ±12,5 years , in the control it was 74 ±13 years. The PM group had slightly more men included (73,2%, n=90), but was not significantly different to the control group (73,2%, n=101. The mean BMI of 26.6 ±4.4 kg/m^2 of the patients in the PM was similar to that of the control group, namely 26.1 ±4.3 kg/m^2.

In the majority of both groups, patients had a coronary heart disease and arterial hypertension diagnosed, the latter however significantly more often in the control group. In both groups, bypass operations, the occurrence of at least one stroke and diabetes type I or II was observed in less than 20% of the patients. Peripheral arterial occlusive disease and aortic valve replacements were observed in less than 10% of the patients in both groups. In less than 2% of the patients in both groups the occurrence of one pulmonary embolism was observed.

In the control group, almost twice the amount of patients (50,7%, n=70) had received a stent implantation making this characteristic significantly different to that in the PM group (26,8%, n=33). In the PM group, roughly one third had been diagnosed with chronic renal insufficiency (31,7%, n=39), whereas in the control group it was about one fifth (21%, n=29). This difference was significant.

Table 6: Baseline Characteristics for Study Population

Baseline Characteristic	PM Group (N=123)	Control Group (N=138)	P-Value[c]
Age in years, mean (SD)	75 (12,5)	74 (13)	0.449[a]
Gender			
Male	90 (73,2%)	101 (73,2%)	1.000[b]
Female	33 (26,8%)	37 (26,8%)	
BMI in kg/m^2, mean (SD)	26.6 ± 4.4	26.1 ± 4.3	0.216[a]
Bypass Operation	21 (17,1%)	15 (10,7%)	0.132[b]
Aortic Valve Replacement	4 (3,3%)	9 (6,5%)	0.227[b]
Stent Implantation	33 (26,8%)	70 (50,7%)	**<0.001[b]**
Coronary Heart Disease	72 (58,5%)	87 (63%)	0.383[b]
Arterial Hypertension	88 (71,5%)	116 (84,1%)	**0.001[b]**
Chronic Renal Insufficiency	39 (31,7%)	29 (21%)	**0.030[b]**
Diabetes Type I or II	23 (18,7%)	16 (11,6%)	0.102[b]
Occurrence of at least one Stroke	14 (11,4%)	19 (13,8%)	0.468[b]
Peripheral Arterial Occlusive Disease	10 (8,1%)	9 (6,5%)	0.798[b]
Occurrence of at least one pulmonary embolism	2 (1,6%)	1 (0,7%)	0.895[b]

[a] p-value from linear mixed model (random intercept model) hat accounts for the matched data (SPSS 24.0)
[b] p-value from binary logistic mixed model (random intercept model) (STATA 15)
[c] significant if p<0.05Table 6 summarizes the baseline data of the study population.
Table 6 lists all the baseline data collected in this study for both the PM and control group.

3. 1. 4. Results included for Comparisons

When comparing the observed data in both groups, the individual control's echocardiographies were only included if the matched patient in the PM group had corresponding data for the equivalent follow-up. Table 7 below summarizes how many echocardiographies were included when comparing results for all examination periods. Echocardiographies were excluded, if the patient's match in the corresponding group did not have an examination in that specific time period.

Table 7: Echocardiographies included for Comparison

		Initial Examination[a]	Follow-Up <1 Month	Follow-Up <12 Months	Follow-Up >1 Year
PM Group	N= total number of echocardiographies available	123	42	47	103
	N= echocardiographies included	**123**	**8**	**34**	**77**
	N= echocardiographies excluded	0	34	13	26
Control Group	N= total number of echocardiographies available	138	19	93	101
	N= echocardiographies included	**138**	**8**	**41**	**85**
	N= echocardiographies excluded	0	11	52	16

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE.
Table 7 shows how many echocardiographies were included for analysis for both groups in this study. Reasons for exclusion are listed in sections 2.3.1. and 2.3.2.

In the PM group, all echocardiographies were included for the pre-implantation observations. In the short-term follow-up, eight patients' results were included, in the mid-term 34 patients' and long-term 77 patient's examinations were included.

In the control group, all echocardiographies were included for the pre-implantation observations. In the short-term follow-up, eight patients' results, in the mid-term 41 patients' and long-term 85 patients' examinations were included.

3. 2. 1. TR Classification

In the tables 8 and 9, the median TR Grades, IQRs and p-values are displayed in each row for both the PM and the control group. Each column represents the follow-up period. Underneath each median (IQR), N (%) of patients who had an examination at that time period is listed. The p-values represent whether a difference in results within a group over time was significant in comparison to the initial TTE.

Table 8: Median TR Grading in the PM Group in Comparison to Initial TTE

PM Group	TTE Pre-Implantation[b]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
TR median[a] (IQR)	1 (1)	1,5 (1)	1 (0,625)	**1 (1)**
p-value[c]		0.102	0.203	**0.041***
N (%) Patients	123 (100%)	8 (6,5%)	34 (28%)	77 (63%)

[a] Medians were calculated using TR Grades as recorded in half steps
[b] The initial examination for the PM group was the TTE before device implantation
[c] p-value from Wilcoxon-Signed Rank Test; compared to initial TTE
* significant if $p<0.05$
Table 8 liststhe median (IQR) of TR Grading for the PM group.

The median TR Classification remained at 1,0 for all follow-up examinations in the PM group, except in the short-term follow-up with 1,5. However, the IQR differed amongst follow-ups starting at 1 for the pre-implantation examination, then 1 at the under one month follow-up, 0,625 at the under 12 months follow-up and lastly 1 at the long-term follow-up. The results for the in the long-term follow-up show a significant difference when compared to the results of the pre-implantation examinations for the PM group.

Table 9: Median TR Grading in the Control Group in Comparison to Initial TTE

Control Group	Initial TTE[b]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
TR median[a] (IQR)	0,75 (0,5)	1,0 (0,75)	0,5 (0,5)	0,5 (0,5)
p-value[c]		0.059	0.062	0.531
N (%) Patients	138 (100%)	8 (6%)	41 (30%)	85 (62%)

[a] Medians were calculated using TR Grades as recorded in half steps
[b] The initial examination for the control group was the chronologically first TTE
[c] p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 9 lists the median (IQR) TR grading for the control group.

The median TR Classification for the control group was 0,75 for the initial TTE. For the consecutive follow-up periods the median TR Classification was 1,0 in the short-term follow-up and remained at 0,5 for the mid-term and long-term follow-up. The IQR remained the same at 0,5 for all follow-up periods in the control group except in the short-term follow-up with 0,75. No significant change within the course of the study was observed.

Table 10 below shows the p-values assessed for comparing the median TR Gradings of the PM group to those of the control group separately for each follow-up interval. The P-values in the bottom row indicate whether the difference between group medians was significant.

Table 10: Median TR Grading and P-Values for PM Group versus Control Group

Group	Initial Examination[a]	Follow-Up < 1 Month	Follow-Up < 12 Months	Follow-Up > 1 Year
PM Group	1,0 (1)	1,5 (1)	1,0 (0,625)	1,0 (1)
Control Group	0,75 (0,5)	1,0 (0,75)	0,5 (0,5)	0,5 (0,5)
p-value	**0.024***	0.140	0.072	**<0.001***

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE.
* significant if $p<0.05$; assessed with a mixed-linear model on SPSS 24.0
Table 10 lists the p-values and significance for the differences in median TR Grading for both groups.

When comparing the two groups, the following observations were made concerning the TR Grading. First, there were marginally more controls included in this study than patients with a PM, however proportionately less controls received a long-term follow-up. Second, the control group's median TR Grading was lower at all examination periods and was significantly lower in the initial examinations and in the long-term follow-ups. Third, the PM group's TR Grading was significantly different within the group long-term TTEs, whereas in the control group no significant change long-term was observed.

3. 2. 2. Change in Tricuspid Valve Function

Pie Charts 1 and 2 show how many patients' TR Grade had changed and in what manner in the long-term follow-up after one year in comparison to the initial TTE. Each pie chart represents echocardiographic findings of the long-term follow up.

Figure 3: Change Pacemaker Group

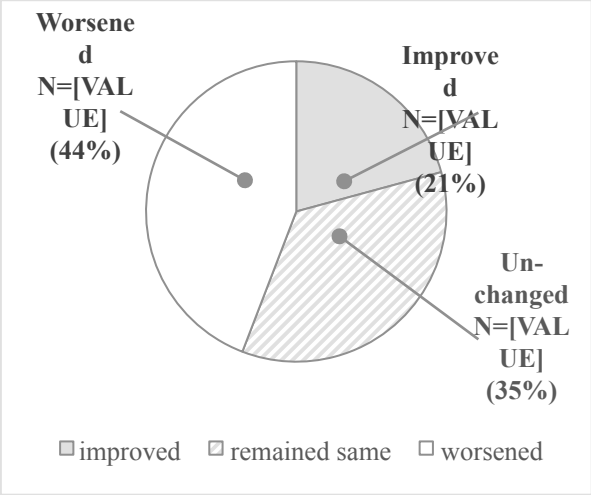


Figure 3: a pie chart showing how many patients' TR Grading in the pacemaker group had worsened, improved or remained unchanged in the long-term follow-ups.

Figure 4: Change Control Group

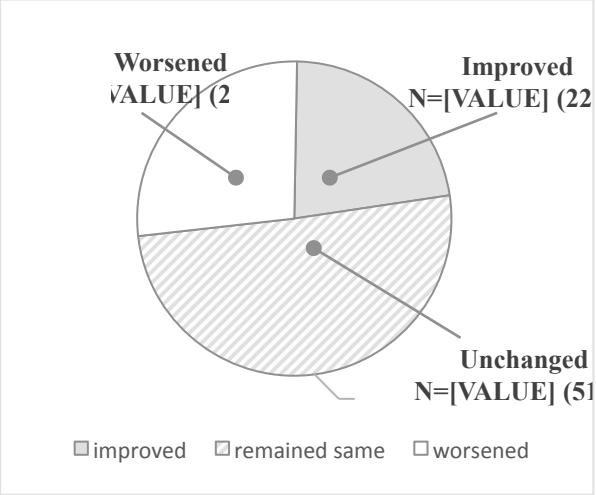


Figure 4: a pie chart showing how many patients' TR Grading in the control group had worsened, improved or remained unchanged in the long-term follow-ups.

In the PM group, a change in TR classification was not observed with 27 patients (35%) at the long-term follow up after at least one year. Of the remaining patients whose grade had changed, 16 (21%) had improved and 34 (44%) had worsened long-term. 46 patients in the PM group either did not have a TTE or their TTE was not included in the long-term follow-up.
In the control group, a change in TR classification was not observed in 43 patients (51%) at the long-term follow up after at least one year. Of the remaining patients whose grade had changed, 19 (22%) had improved and 23 (27%) had worsened long-term. 53 patients in the PM group either did not have a TTE or their TTE was not included in the long-term follow-up

Proportionately, more patients worsened in TR Grading in the PM group over time. However, more patients remained the same in TR Grading in the control group over time. A similar portion of patients improved in TR Grading in both groups.

3. 2. 3. How the Tricuspid Valve Function changed in the PM Group

Bar graph 1 below shows how the TR gradings were distributed amongst the pre-implantation examinations (left column) and the long-term follow-up (right column) for the PM group. The arrows represent who changed and in what manner for each classification, the number of patients is labelled accordingly. In this figure, gradings were summarized in the common TR classification system as 0, I, II, III for overview purposes.

In the pre-implantation TTEs, 6% (n=7) of patients had a TR grade 0. Of these patients, two patients (29%) worsened by one grade and one patient worsened by three grades. (14%). Four of these patients (57%) did not have a long-term follow up.

69% (n=85) of the patients had a TR grade of I initially. Of these patients, one (1%) improved by one grade, 41 (48%) remained the same, 10 (12%) worsened by one grade and two (2%) patients worsened by two grades. 31 of these Patients (36%) did not have a long-term follow-up.

21% (n=26) of the patients had a TR Grade of II initially. Of these patients, 10 (38%) improved by one grade, six (23%) remained the same and two (8%) patients worsened by one grade. Of these patients, 8 (31%) did not have a long-term follow-up.

4% (n=5) of the patients had a TR Grade of III initially. Of these patients, one (20%) improved by one grade and one (20%) remained the same. Three of these patients (60%) did not have a long-term follow up.

Thus, the distribution of TR grades amongst the 77 echocardiographic long-term follow-ups after at least one year after implantation in the PM group was: 1% (n=1) had a TR 0°, 69% (n=53) had a TR I°, 22% (n=17) had a TR II° and lastly 8% (n=6) had a TR III°.

Figure 5: Bar Graph showing how TR Grading Changed Long-Term in the PM Group

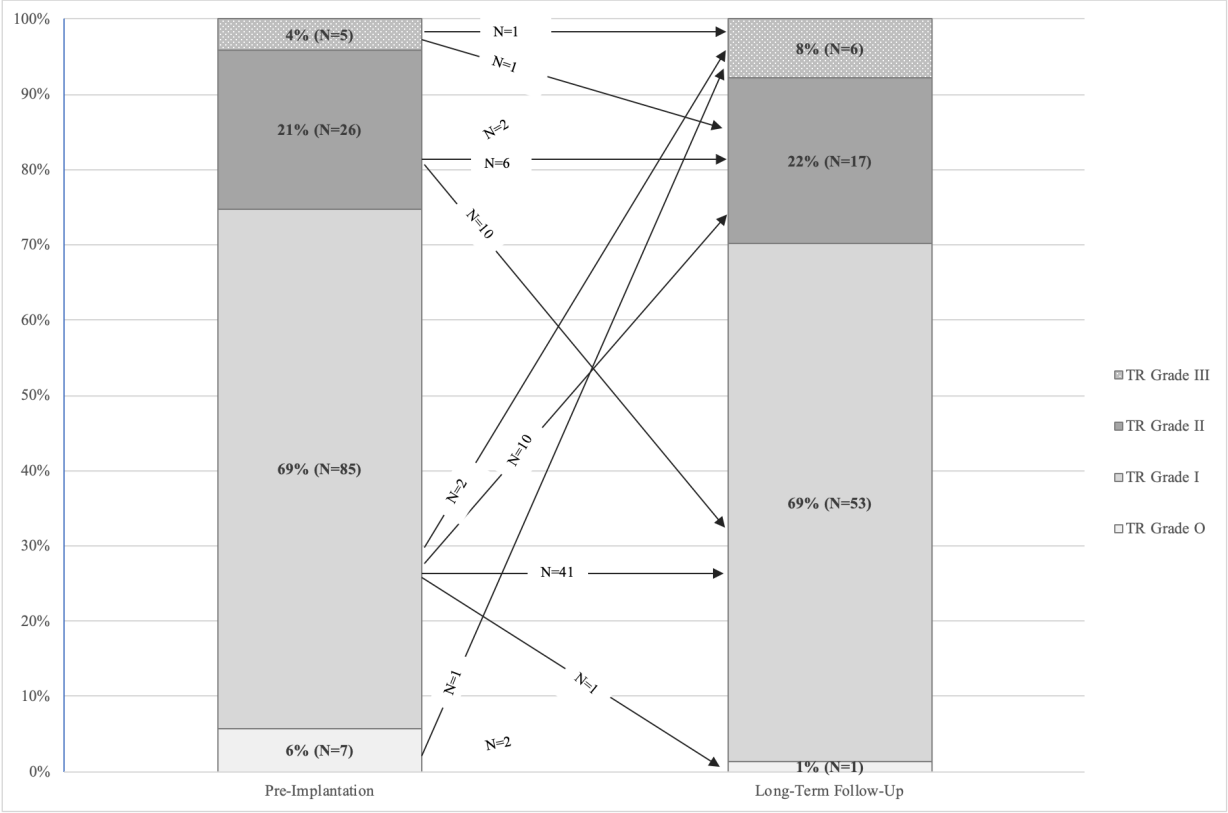


Figure 5 is a bar graph depicting the distribution of TR Grading in the PM group during the initial TTE and how it changed in the long-term follow-up.

3. 2. 4. How the Tricuspid Valve Function changed in the Control Group

Bar graph 2 below shows how the TR gradings were distributed amongst the initial examinations (left column) and the long-term follow-up (right column) for the control group. The arrows represent who changed and in what manner for each classification, the number of patients is labelled accordingly. In this figure, gradings were summarized in the common TR classification system as 0, I, II, III for overview purposes.

In the initial TTEs, 12% (n=17) of the controls had a TR grade 0. Of these patients, three (18%) remained the same and nine (53%) worsened by one grade. Five patients (29%) did not have a long-term follow-up.

73% (n=101) of the controls had a TR grade I initially. Of these patients, 57 (56%) remained the same and four (4%) worsened by one grade. 40 patients (40%) did not have a long-term follow-up.

11% (n=15) of the controls had a TR grade II initially. Of these patients, four (26,6%) improved by one grade and five (33,3%) remained the same. Six of these patients (40%) did not have a long-term follow up.

4% (n=5) of the controls had a TR grade III initially. Of these patients, one (20%) improved by one grade and two (40%) remained the same. Two patients (40%) did not have a long-term follow up.

Thus, the distribution of TR grades amongst the total 85 echocardiographic long-term follow-ups in the control group was: 4% (n=3) had TR 0°, 82% (n=70) had TR I°, 12% (n=10) had TR II° and lastly 2% (n=2) had TR III°.

Figure 6: Bar Graph showing how TR Grading Changed Long-Term in the Control Group

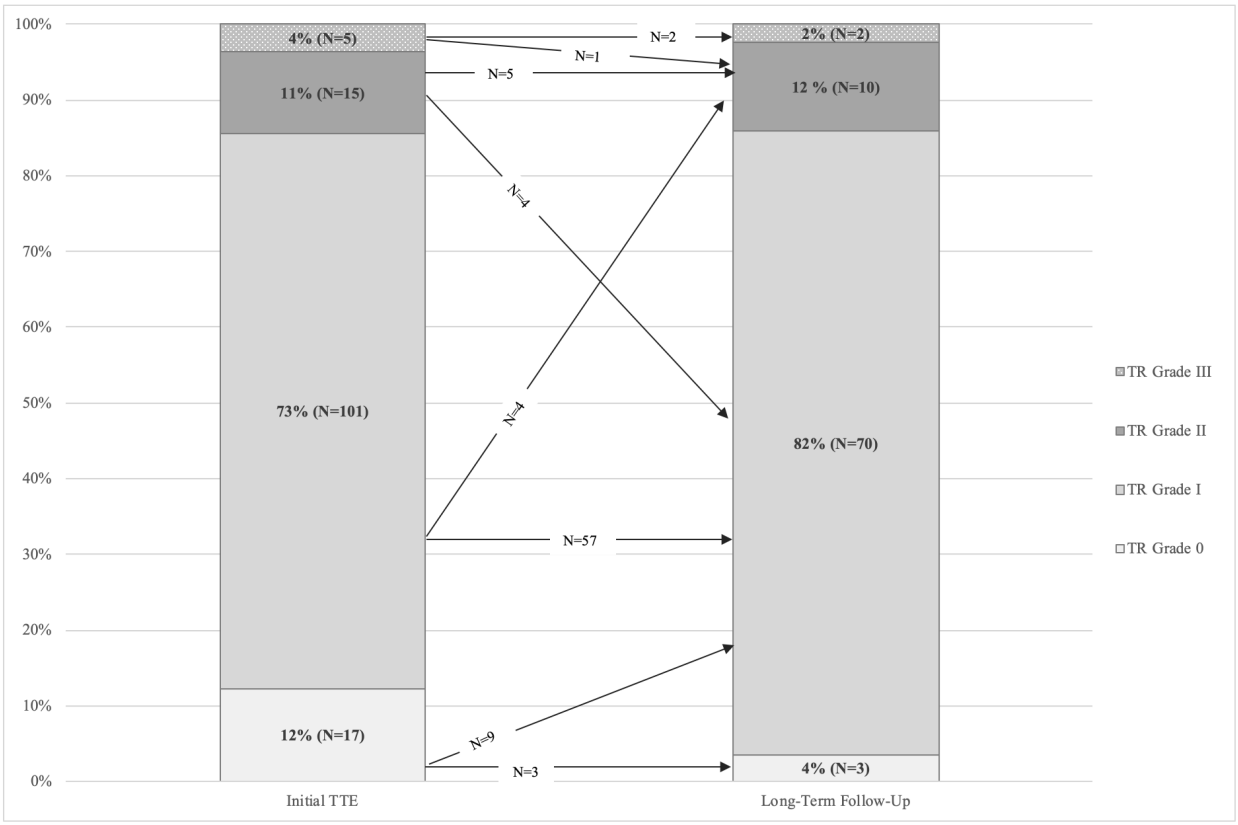


Figure 6 shows a bar graph depicting the distribution of TR Grading in the control group during the initial TTE and how it changed in the long-term follow-up.

3. 3. Other echocardiographic Values

3. 3. 1. TR Vmax

Tables 11 and 12 below display the mean TR Vmax m/s and standard deviation for each group separately. Each column represents the results for the follow-up period consecutively from right to left. The rows represent the mean values, p-values and n (%) patients for each follow-up period. The p-values represent whether a difference in results within a group over time were significant in comparison to the initial TTE.

Table 11: Mean TR Vmax m/s in the PM Group in Comparison to the Initial TTE

PM Group	TTE Pre-Implantation[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
TR Vmax m/s mean (SD)	2,59 (0,72)	2,8 (0,27)	2,71 (0,59)	2,66 (0,54)
p-value[b]		0.803	0.080	0.619
N (%) Patients	123 (100%)	8 (6,5%)	34 (28%)	77 (63%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 11 lists the mean TR Vmax for the PM group.

The mean TR Vmax in the pre-implantation examinations for the PM group was 2,59 ±0,72 m/s. Within the first month after implantation it was 2,8 ±0,27 m/s. Within 12 months after implantation the mean lay at 2,71 ±0,59 m/s. In the long-term follow-ups, the mean TR Vmax for the PM group was 2,66 ±0,54 m/s. The changes in TR Vmax over time were not significant within the PM group.

Table 12: Mean TR Vmax m/s in the Control Group in Comparison to the Initial TTE

Control Group	Initial TTE[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
TR Vmax m/s mean (SD)	2,56 (0,70)	2,35 (0,50)	2,61 (0,60)	2,60 (0,60)
p-value[b]		0.063	0.213	0.490
N (%) Patients	138 (100%)	8 (6%)	41 (30%)	85 (62%)

[a]The initial examination for the control group was the chronologically first TTE
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 12 lists the mean TR Vmax for the PM group.

The mean TR Vmax for the control group in the initial examinations was 2,56 ±0,70 m/s. In the short-term follow-up within one month afterwards, the mean was 2,35 ±0,50 m/s. Within 12

months afterwards, the mean lay at 2,61 ±0,60 m/s. In the long-term follow-up, the mean TR Vmax for the control group was 2,60 ±0,60 m/s.

The mean TR Vmax increased significantly within the mid-term follow-up, however no significant change was observed long-term.

Table 13 below shows the p-values when comparing the mean TR Vmax m/s of the PM group to those of the control group separately for each follow-up interval.

Table 13: Mean TR Vmax (m/s) and P-Values for PM Group versus Control Group

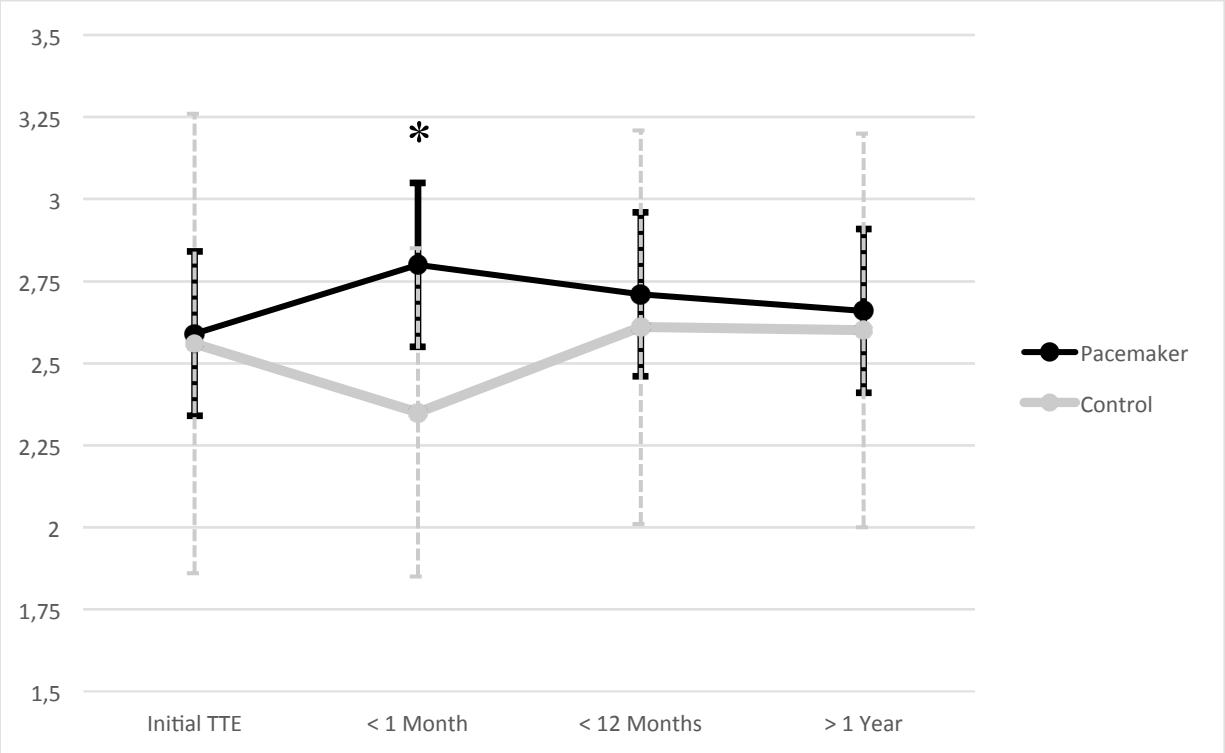
TR Vmax (Mean±SD)	**Initial Examination [a]**	**Follow-Up < 1 Month**	**Follow-Up < 12 Months**	**Follow-Up > 1 Year**
PM Group	2,59 ±0,72	2,8 ±0,27	2,71 ±0,59	2,66 ±0,54
Control Group	2,56 ±0,70	2,35 ±0,50	2,61 ±0,60	2,60 ±0,60
p-value	0.673	**0.014***	0.469	0.530

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE
* significant if $p<0.05$; assessed with a mixed-linear model on SPSS 24.0
Table 13 lists the different mean TR Vmax for both groups and whether these differences were significant.

The mean TR Vmax was significantly higher in the exposure group during the short-term follow-ups. No other differences between the groups were significant.

Line graph 1 shows the mean values and their standard deviations for the TR Vmax observed in the PM and the control group. The means for each follow-up period are displayed. The x axis represents the time periods, the y axis represents the TR Vmax measurement in mm.

Figure 7: TR Vmax (m/s) Mean and Standard Deviation



* significant if $p<0.05$
Figure 7 shows a line graph marking the mean TR Vmax of the PM in comparison to the PM group.

When comparing the two groups, the following observations were made concerning the TR Vmax m/s. The mean TR Vmax of the PM group was greater at every follow-up period. However, the PM group had a significantly higher TR Vmax only short-term. For both the PM and control group, no significant change was observed within each group long-term.

3. 3. 2. TAPSE

Tables 14 and 15 display the mean TAPSE mm and standard deviation for each group separately. Each column represents the results for the follow-up period consecutively from right to left. The rows represent the mean values, p-values and n (%) patients for each follow-up period. The p-values represent whether a difference in results within a group over time were significant in comparison to the initial TTE.

Table 14: Mean TAPSE mm in the PM Group in Comparison to the Initial TTE

PM Group	TTE Pre-Implantation[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
TAPSE mm Mean (SD)	21,72 (5,87)	19,7 (8,0)	22,18 (5,16)	21,57 (5,54)

p-value[b]		0.575	0.861	0.803
N (%) Patients	123 (100%)	8 (6,5%)	34 (28%)	77 (63%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if p<0.05
Table 14 lists the mean TAPSE for the PM group.

The mean TAPSE in the pre-implantation examinations for the PM group was 21,72 ±5,87 mm. Within the one-month follow-up, the mean was 19,7 ±8,0 mm. Within the 12-month follow-up, the mean was 22,18 ±5,16 mm. The mean TAPSE for the PM group in the long-term follow-ups was 21,57 ±5,54 mm. No significant change in the mean TAPSE within the PM group was observed.

Table 15: Mean TAPSE mm in the Control Group in Comparison to the Initial TTE

Control Group	**Initial TTE**[a]	**Follow-Up < 1 Month**	**Follow-Up <12 Months**	**Follow-Up > 1 Year**
TAPSE mm mean (SD)	23,75 (4,89)	23,22 (4,66)	24,55 (5,50)	23,45 (4,47)
p-value[b]		0.397	0.560	0.620
N (%) Patients	138 (100%)	8 (6%)	41 (30%)	85 (62%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if p<0.05
Table 15 lists the mean TAPSE for the control group
The mean TAPSE for the control group in the initial examinations was 23,75 ±4,89 mm. The mean in the one-month follow-up was 23,22 ±4,66 mm. The mean in the 12-month follow-up was 24,55 ±5,50 mm. The mean TAPSE for the control group in the long-term follow-ups was 23,45 ±4,47 mm. No significant change in mean TAPSE was observed within the control group.

Table 16 below shows the p-values when comparing the mean TAPSE mm of the PM group to those of the control group separately for each follow-up interval.

Table 16: Mean TAPSE (mm) and P-Values for PM Group versus Control Group

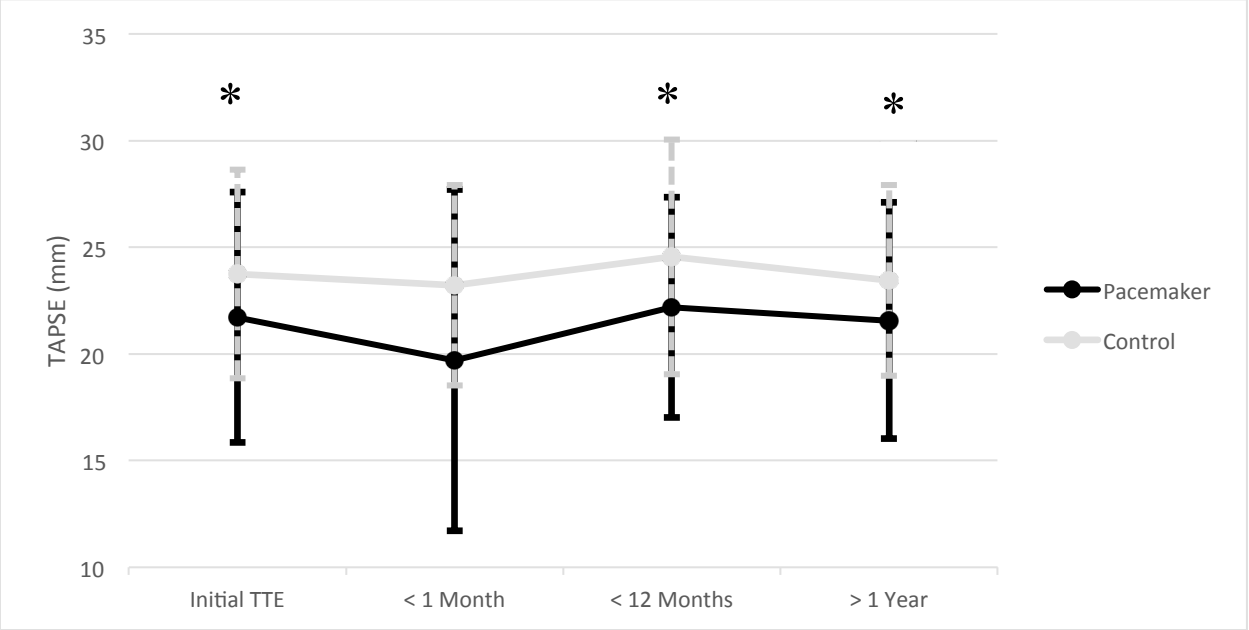
TAPSE Mean±SD	Initial Examination [a]	Follow-Up < 1 Month	Follow-Up < 12 Months	Follow-Up > 1 Year
PM Group	21,72 ±5,87	19,7 ±8,0	22,18 ±5,16	21,57±5,54
Control Group	23,75 ±4,89	23,22±4,7	24,55 ±5,50	23,45 ±4,47
p-value	**0.002***	0.211	**0.043***	**0.018***

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE
* significant if p<0.05; assessed with a mixed-linear model on SPSS 24.0

Table 16 lists the different mean TAPSE for both groups and whether these differences were significant.

Additionally, Line graph 2 shows the mean values and their standard deviations for the TAPSE observed in the PM and the control group and summarized in Table 16. The means for each follow-up period are displayed. The x axis represents the time periods, the y axis represents the TAPSE measurement in mm.

Figure 8: TAPSE (mm) Mean and Standard Deviation



* significant if $p<0.05$
Figure 8 shows a line graph that depicts the different mean TAPSE for both groups.

When comparing the two groups, the following observations were made regarding the TAPSE. First, no changes within both groups were significant. However, the mean TAPSE of the control group was greater at every follow-up period. The control's TAPSE was significantly greater in the initial examinations, in the mid-term and in the long-term follow-up.

3. 3. 3. LVEF

Tables 17 and 18 display the mean LVEF % and standard deviation for each group separately. Each column represents the results for the follow-up period consecutively from right to left. The rows represent the mean values, p-values and n (%) patients for each follow-up period. The p-values represent whether a difference in results within a group over time were significant in comparison to the initial TTE.

Table 17: Mean LVEF% in the PM Group in Comparison to the Initial TTE

PM Group	TTE Pre-Implantation[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
LVEF % Mean (SD)	46,6 (19,6)	**44,2 (13,7)**	50,7 (17,1)	48,4 (15,9)
p-value[b]		0.109	0.120	0.344
N (%) Patients	123 (100%)	8 (6,5%)	34 (28%)	77 (63%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 17 lists the mean LVEF for the PM group for all examination periods.

The LVEF for the PM group averaged at 46,6 ±19,6% before implantation. The mean LVEF in the first two follow-ups was 44,7 ±15,0% and 50,7 ±17,1%. However, it averaged at 48,4 ±15,9% in the long-term follow up being slightly larger than pre-implantation. Within the PM group, the average LVEF did not significantly change by the end of this study.

Table 18: Mean LVEF% in the Control Group in Comparison to the Initial TTE

Control Group	Initial TTE[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
LVEF % Mean (SD)	59,1 (13,7)	54,78 (15,3)	60,0 (11,9)	62,9 (9,5)
p-value[b]		**0.008***	**0.022***	0.188
N (%) Patients	138 (100%)	8 (6%)	41 (30%)	85 (62%)

[a]The initial examination for the control group was the chronologically first TTE
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 18 lists the mean LVEF for the control group for all follow-up periods.

The controls' initial mean LVEF was 59,1 ±13,7%, followed by 54,78 ±15,3%, 60,0 ±11,9% and lastly averaged at 62,9 ±9,5 % at the long-term follow-up. LVEF averaged significantly less in the first follow-up ($p=0.008$) and improved again significantly in the second follow-up ($p=0.022$) when compared to the initial TTE.

Table 19 below shows the p-values assessed when comparing the mean LVEF % of the PM group to those of the control group separately for each follow-up interval.

Table 19: Mean LVEF (%) and P-Values for PM Group versus Control Group

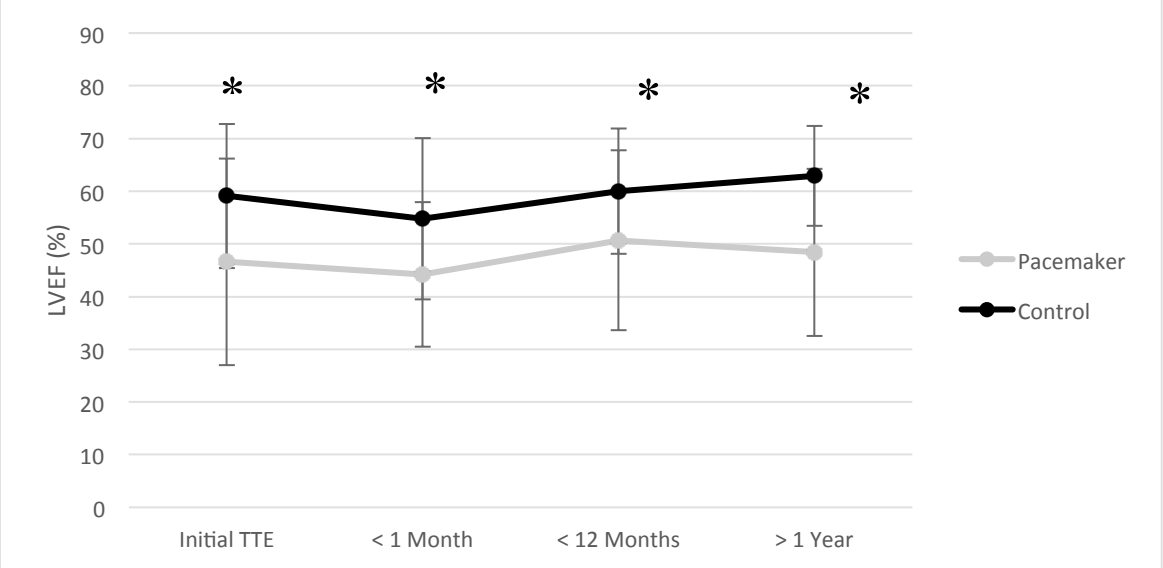
LVEF Mean±SD	Initial Examination [a]	Follow-Up < 1 Month	Follow-Up < 12 Months	Follow-Up > 1 Year
PM Group	46,6 ±19,6	44,2 ±13,7	50,7 ±17,1	48,4 ±15,9
Control Group	59,1 ±13,7	54,78 ±15,3	60,0 ±11,9	62,9 ±9,5

p-value	**<0.001***	**0.004***	**0.001***	**<0.001***

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE
* significant if p<0.05; assessed with a mixed-linear model on SPSS 24.0
Table 19 lists the different mean LVEF for both groups and whether these differences were significant.

The mean LVEF was significantly greater in the control group at every follow-up period.
Line graph 3 shows the mean values and their standard deviations for LVEF observed in the PM and the control group. The means for each follow-up period are displayed. The x axis represents the time periods, the y axis represents the LVEF measurement in %.

Figure 9: LVEF % Mean and Standard Deviation



* significant if p<0.05
Figure 9 shows a line graph depicting the mean LVEF for both groups.

When comparing the PM and control group, the following observations were made regarding LVEF. Both group's LVEF worsened significantly short-term. The control groups' mean LVEF improved significantly mid-term again.

The control group's mean LVEF was significantly greater than that of the PM group at every time period. However, there was no significant change long-term in both groups.

3. 3. 4. Right Atrium Volume

Tables 20 and 21 display the mean RA volume in ml and standard deviation for each group separately. Each column represents the results for the follow-up period consecutively from right to left. The rows represent the mean values, p-values and n (%) patients for each follow-up

period. The p-values represent whether a difference in results within a group over time were significant in comparison to the initial TTE.

Table 20: Mean RA Volume (ml) in the PM Group in Comparison to the Intial TTE

PM Group	TTE Pre-Implantation[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
RA Volume (ml) Mean (SD)	51,7 ±24,9	49,8 ±33,8	54,8 ±33,5	62.3 ±37,7
p-value[b]		0.917	0.480	0.054
N (%) Patients	123 (100%)	8 (6,5%)	34 (28%)	77 (63%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 20 lists the mean RA volume for the PM group for all follow-up periods.

The mean RA volume in the PM group's initial examinations was 51,7 ±24,9ml, followed by 49,8 ±33,8ml short-term, 54,8 ±33,5ml mid-term and averaged at 62.3 ±37,7ml in the long-term follow-ups. There was no significant change in RA volume in the PM group over time.

Table 21: Mean RA Volume (ml) in the Control Group in Comparison to the Intial TTE

Control Group	Initial TTE[a]	Follow-Up < 1 Month	Follow-Up <12 Months	Follow-Up > 1 Year
RA Volume (ml) Mean (SD)	44,0 ±30,1	75,7 ±58,7	47,1 ±29,5	51,7 ±44,5
p-value[b]		0.465	0.657	0.821
N (%) Patients	138 (100%)	8 (6%)	41 (30%)	85 (62%)

[a]The initial examination for the PM group was the TTE before device implantation
[b]p-value from Wilcoxon-Signed Rank Test, compared to initial TTE
* significant if $p<0.05$
Table 21 lists the mean RA volume for the control group for all examination periods.

The control group's initial average RA volume was 44,0 ±30,1ml. Within the first month afterwards the mean lay at 75,7 ±58,7ml, was 47,1 ±29,5ml within one year afterwards and averaged at 51,7 ±44,5ml in the long-term follow-up. The was no significant change in RA volume in the control group over time.

Table 22 below shows the p-values assessed when comparing the mean RA volume in ml of the PM group to those of the control group separately for each follow-up interval.

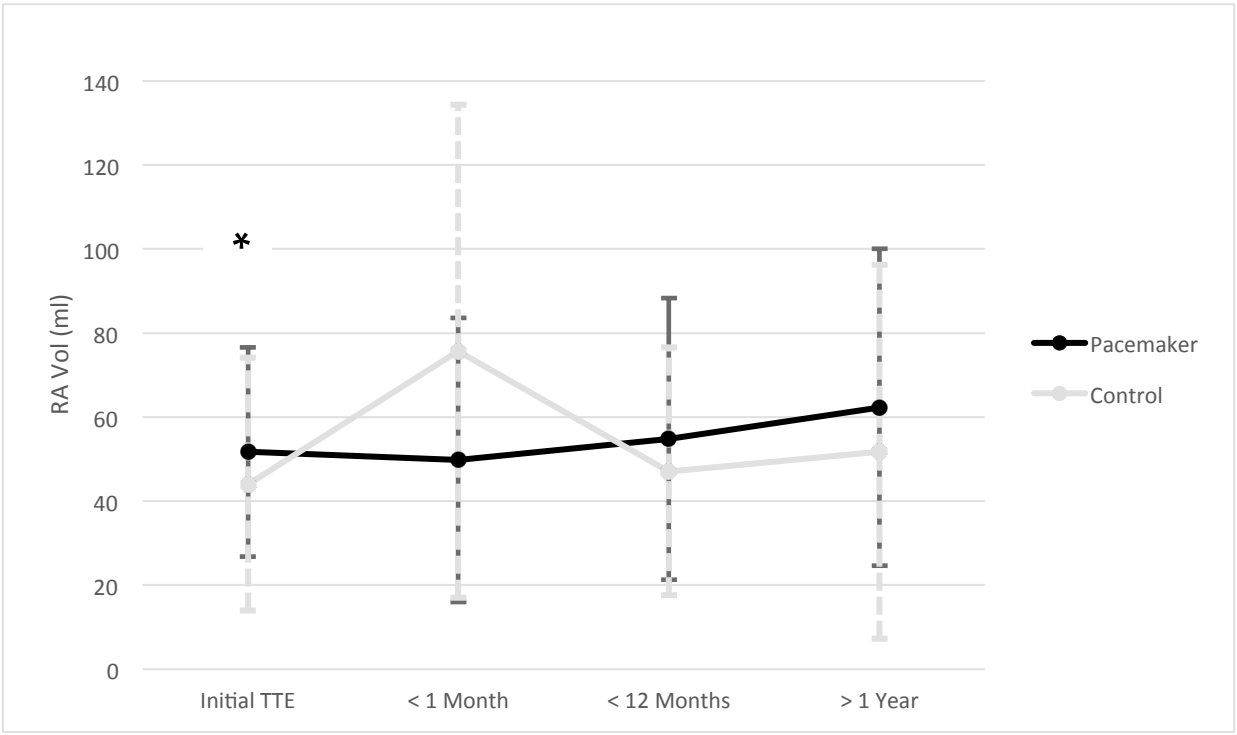
Table 22 Mean RA Volume (ml) and P-Values for PM Group versus Control Group

RA Volume Mean±SD	Initial Examination [a]	Follow-Up < 1 Month	Follow-Up < 12 Months	Follow-Up > 1 Year
PM Group	51,7 ±24,9	49,8 ±33,8	54,8 ±33,5	62.3 ±37,7
Control Group	44,0 ±30,1	75,7 ±58,7	47,1 ±29,5	51,7 ±44,5
p-value	**0.018***	0.207	0.482	0.101

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE
* significant if p<0.05; assessed with a mixed-linear model on SPSS 24.0
Table 22 lists the different mean RA volume for both groups and whether these differences were significant.

Line graph 4 shows the mean values and their standard deviations summarized in table 22 for RA volume observed in the PM and the control group. The means for each follow-up period are displayed. The x axis represents the time periods, the y axis represents the RA volume measurement in ml.

Figure 10: RA Volume (ml) Mean and Standard Deviation



* significant if p<0.05
Figure 10 shows a line graph markig the mean RA volume for both groups.

When comparing the two groups, the PM group's mean RA volume was only significantly greater in the initial TTEs. Within both groups however, no significant alteration in RA volume occurred.

3. 3. 5. All Echocardiographic Values

Table 23 summarizes the median values, IQRs, mean values, standard deviations and absolute frequencies for all of the echocardiographic data observed in this study. The Table lists all data for both the PM as well as the control group. Each column represents the specific follow-up period. Each row represents the data for the PM and control group alternately.

The values described in this table from top to bottom are: TR Grade, TR Vmax in m/s, TAPSE in mm, LVEF in %, the recorded SPAP in mmHG, the calculated SPAP in mmHg, CVP in mmHG and lastly how often a widened vena contracta had been observed.

The values marked with an asterisk are the values that were significantly different ($p<0.05$) when comparing the results between the PM and control group.

Table 23: Summary Table for all other Echocardiographic Values for the PM and Control Group

Echocardiographic Variable	Group[a]	Initial TTE[b]	Follow-Up <1 Month	Follow-Up <12 Months	Follow-Up >1 Year
PISA (mm) mean (SD)	PM	5,4 (1,8)	5,7 (2,0)	6,2 (2,6)	5,4 (1,9)
	Control	5,2 (2,0)	7,3 (3,0)	7,0 (2,7)	5,3 (2,1)
SPAP Recorded (mmHg) mean (SD)	PM	36,6 (11,6)	35,4 (9,5)	36,5 (10,2)	35,3 (9,7)
	Control	34,2 (14,0)	30,3 (9,4)	32,7 (15,8)	32,4 (11,4)
SPAP Calculated (mmHg) Mean (SD)	PM	34,2 (14,2)	37,4 (6,9)	36,5 (12,1)	35,0 (11,1)
	Control	33,4 (15,7)	**29,8 (10,6)***	34,1 (14,2)	33,0 (13,2)
CVP (mmHg) mean (SD)	PM	5,5 (1,7)	5,8 (2,0)	5,7 (1,7)	5,7 (2,1)
	Control	5,4 (1,7)	6,7 (3,5)	5,3 (1,2)	**5,1 (0,8)***
Vena Contracta Width (mm) Mean (SD)	PM	5,6 (1,6)	5,4 (2,8)	5,2 (2,1)	5,0 (1,7)
	Control	5,1 (1,6)	9,3 (3,8)	5,8 (1,8)	6,2 (7,1)

[a] PM Group N=123; Control Group N=138

[b] The initial examination for the PM group was the TTE before device implantation; the initial examination for the control group was the chronologically first TTE

*significant if $p<0.05$; assessed with a mixed-linear model on SPSS 24.0

Table 23 shows the mean values for other echocardiographic values used to indirectly asses TR. Here the averages of the PM and control group are compared statistically to one another and marked accordingly if significantly different.

The values for the median TR Grade, mean TR Vmax, mean TAPSE and mean LVEF are described in the section above.

The mean PISA in the PM group hardly differed within the course of this study. Initially it was 5,4 ±1,8 mm, in the first follow-up it was 5,7 ±2,0 mm, mid-term it was 6,2 ±2,6 mm, and lastly averaged at 5,4 ±1,9 mm in the long-term follow-up. The control group's initial mean PISA was 5,2 ±2,0 mm, was 7,3 ±3,0 mm short-term, was 7,0 ±2,7mm mid-term and was lastly 5,3 ±2,1 mm in the long-term follow-up. The differences between both groups were not significant at any examination period.

The mean recorded SPAP for the PM group differed slightly throughout follow-ups. The initial mean was 36,6 ±11,6 mmHg, followed by 35,4 ±9,5 mmHg, 36,5 ±10,2 mmHg and averaged at 35,3 ±9,7 mmHg in the long-term follow up. The lowest mean recorded SPAP was observed in the one-month follow up for both groups. The control group's initial mean recorded SPAP was 34,2 ±14,0 mmHg, followed by 30,3 ±9,4 mmHg, 32,7 ±15,8 mmHg and averaged at 32,4 ±11,4 mmHg. The controls' recorded SPAP was on average lower than that of the PM group at each follow-up and but not significantly lower at any follow up.

The mean calculated SPAP for the PM group differed throughout follow-ups as well. The initial mean was 34,2 ±14,2 mmHg, followed by 37,4 ±6,9 mmHg, 36,5 ±12,1 mmHg and averaged at 35,0 ±11,1 mmHg long-term. The lowest mean calculated SPAP was observed initially in the PM group, and at the one-month follow up for the control group. The control group's initial calculated SPAP mean was 33,4 ±15,7 mmHg, followed by 29,8 ±10,6 mmHg, 34,2 ±14,2 mmHg and averaged at 33,0 ±13,2 mmHg in the long-term follow-up. The controls' calculated SPAP was on average lower than that of the PM group at each follow-up. The control group's lower mean calculated SPAP was only significant in the short-term follow-up.

The mean CVP for the PM group initially was 5,5 ±1,7 mmHg, followed by 5,8 ±2,0 mmHg, 5,7 ±1,7 mmHg and lastly 5,7 ±2,1 mmHg. The control group's mean CVP initially was 5,4 ±1,7 mmHg, followed by 6,7 ±3,5 mmHg, 5,3 ± 1,2 mmHg and lastly 5,1 ±0,8 mmHg. The control group's mean CVP was significantly lower in the long-term follow-up.

The mean vena contracta width in the PM group initially was 5,6 ±1,6mm, was 5,4 ±2,8mm short-term, was 5,2 ±2,1 mm mid-term and 5,0 ±1,7 mm in the long-term follow-up. The control group's mean vena contracta width was initially 5,1 ±1,6 mm, followed by 9,3 ±3,8 mm short-term, was 5,8 ±1,8 mm mid-term and was lastly 6,2 ±7,1 mm long-term. The differences between the two groups were not significant at any examination period.

3.4. Tests for Significance Differences

In order to establish whether the differences in medians and means between the PM and control group were statistically significant, a mixed linear model for paired variables on SPSS Version 24.0 was performed. Here the results of both groups were compared to each other for each follow-up period. Table 24 below summarizes the output of each test. Each column represents the different follow-up periods. Each row represents the characteristic analyzed with the according p-value. In this Test, the TR classification used was as recorded for the study in half steps.

Table 24: P-Values for each Variable PM versus Control

* significant if p<0.05; assessed with a mixed-linear model on SPSS 24.0

Variable	Initial Examination[a]	Follow-Up < 1 Month	Follow-Up < 12 Months	Follow-Up > 1 Year
TR Grading[b]	**0.024***	0.140	0.072	**<0.001***
TR Vmax (m/s)	0.673	**0.014***	0.469	0.530
TAPSE (mm)	**0.002***	0.211	**0.043***	**0.018***
LVEF (%)	**<0.001***	**0.004***	**0.001***	**<0.001***
RA Volume (ml)	**0.018***	0.353	0.283	0.101
PISA (mm)	0.613	0.220	0.559	0.877
SPAP recorded (mmHg)	0.175	0.188	0.197	0.112
SPAP calculated (mmHg)	0.647	**0.035***	0.367	0.287
CVP (mmHg)	0.754	0.612	0.276	**0.017***
Vena Contracta Width (mm)	0.168	0.219	0.514	0.346

[a] The initial examinations for the PM group were pre-implantation. The initial examination for the control group were the patients' chronologically first TTE.
[b] TR Grading in this Test was kept in half steps as recorded in this study.

Table 24 summarizes all the p-values assessed for comparing the specific echocardiographic data of the PM and the control group and marked accordingly if significant.

The difference in TR grading between the PM and control group was statistically significant in the initial Examination (p= 0.021) and within the long-term follow-up (p=<0.001). The differences in mean TR Vmax were significant in the short-term follow-up (p=0-.014). The difference in TAPSE observations between both groups was statistically significant in the initial examination (p=0.001), in the 12-motnh follow-up (p=0.009) and in the long-term follow-up (p=0.001). The difference in LVEF observations between both groups was statistically significant in all examination periods (p= <0.001, 0.003, <0.001 and <0.001). The difference in RA Volume was significant in the initial examination (p=0.018). The differences in PISA were not significantly different at any examination period. The difference in SPAP as recorded by examiners was not statistically significant in any examination period. The difference in SPAP as calculated in this study was statistically significant in the short-term follow-up (p=0.035). The difference in CVP observation for both groups was statistically significant in the long-term follow-up (p=0.017). The differences in vena contracta width were not significantly different at any examination period.

3. 5. Survival

3. 5. 1. Overall Survival

The enquiry was made for all 261 patients included in this study, namely the 123 patients in the PM group and the 138 Patients in the control group. On the date of the granted enquiry, information was provided for a total of 226 (87%) patients. Of these 226 patients, 71 (31%) had been registered as deceased. For the remaining 35 (13%) no information was provided.

Bar graph 3 below shows how many people were registered as alive, deceased and for how many patients no information was provided for both the PM group and control group separately on the date of the granted enquiry. Reasons for why no information could be provided are described in section 2.7.2. In the bar graph below, the X axis represents the group and information provided accordingly. The y-axis represents the percentage of patients pertaining to each group. Each bar's data is labelled on top with the absolute number of patients in parenthesis.

Figure 11: Overall Survival of PM and Control Group

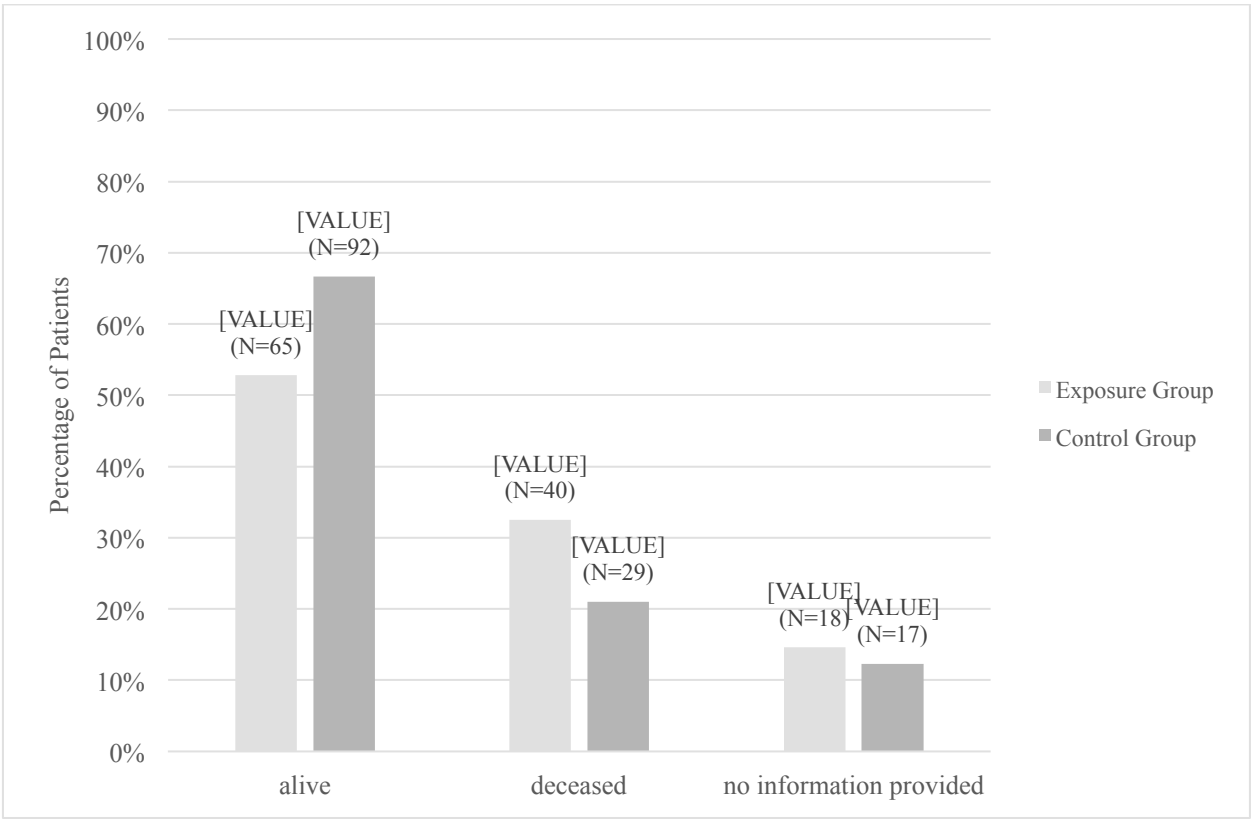


Figure 11 depicts the absolute amount of patients in this study who had been registered as deceased, alive or to whom no information was provided for in 2018 in Berlin Germany, enquired at the Landesamt für Bürger- und Ordnungsangelegenheiten Berlin, Germany (State Office for Residents' and Regulatory Affairs).

In the PM group, 52,8 % (N=65) of the patients were registered as alive, 32,5% (N=40) as deceased and for 14,6% (N=18) no information was provided. In the control group, 66,7% (N=92) of the patients were registered as alive, 21,0% (N=29) as deceased and for 12,3% (N=17) no information was provided. Proportionately, less people were registered as alive and more as deceased in the PM group.

3. 5. 2. Kaplan-Meier Estimate

Figure 3 displays a Kaplan-Meier estimate. The graph shows two functions, each one representing the PM or control group. The x-axis represents the time in years. The y axis represents the cumulative survival probability of the patients. Each cross on a line represents when a single or multiple patients were censored. The graph also shows that the observation period in this study was about eight years.

Figure 12: Kaplan-Meier Estimate

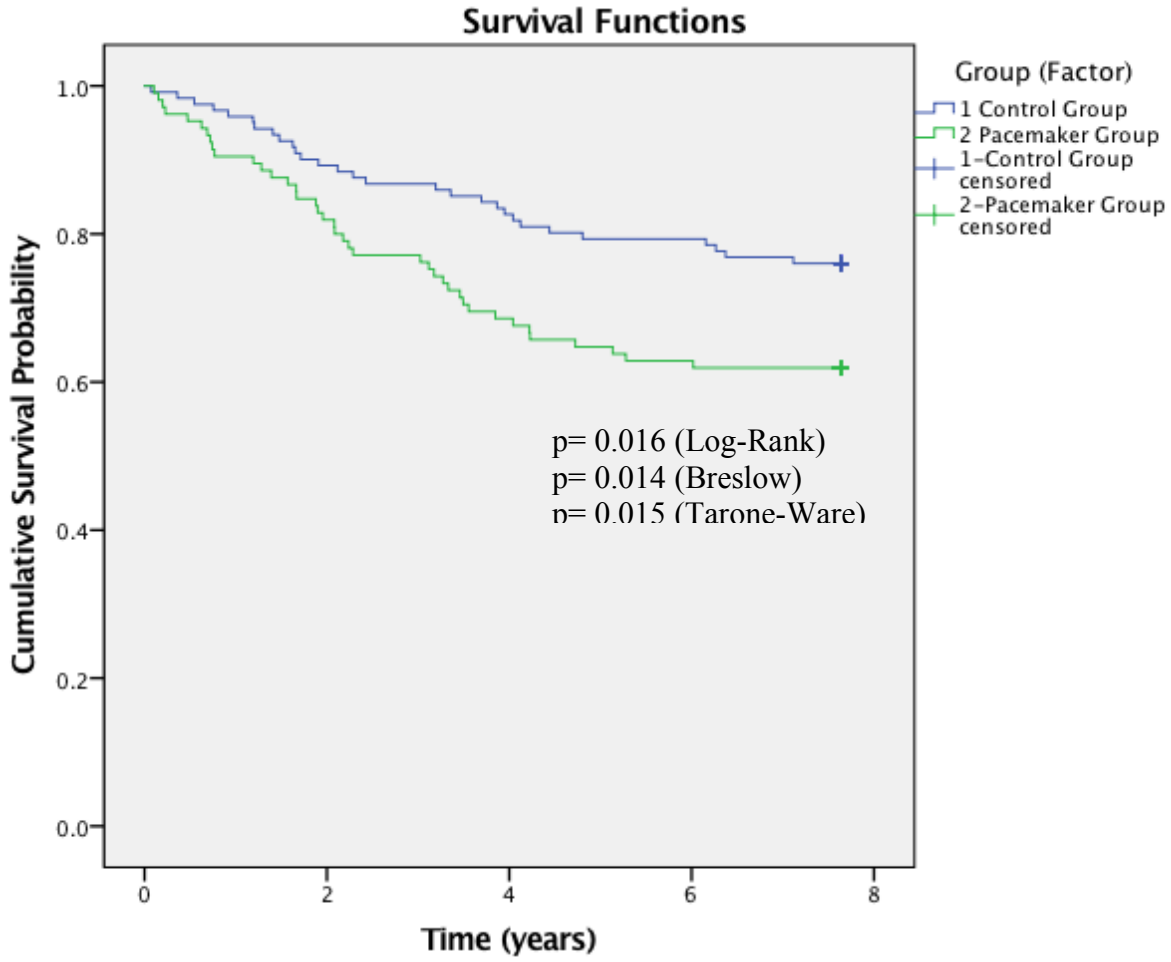


Figure 3 shows the Kaplan Meier Estimate as a cumulative survival function over time. It reveals that the PM group had a significantly lower cumulative survival probability.

Additionally, the output results from SPSS are shown below in Table 25.

Table 25: Output SPSS Kaplan-Meier

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	5.770	1	.016
Breslow (Generalized Wilcoxon)	6.041	1	.014
Tarone-Ware	5.926	1	.015

Test of equality of survival distributions for the different levels of Group (Factor)

Table 25 is an original output calculated in this study and lists the specific information for the significance calculation.

The Kaplan-Meier survival curve shows that the patients in the PM group had a significantly lower estimated cumulative survival probability of roughly 61%. The control group's estimated cumulative survival probability was around 78%. The three tests used to analyse the difference in cumulative survival probabilities show that the difference was significant (p=0.016, p= 0.014, p=0.015). Censored patients only occurred at the ending date of the observation, as the study was conducted retrospectively and no patients dropped out during the observation period.

Discussion

4. 1. Major Findings

The findings in this study suggest that the right and left heart function in patients, who had received a cardiac rhythm device, remained stable. The observations infer that TR did not principally worsen after device implantation. The findings pertaining to TAPSE, RA volume and CVP indicate that patients with a cardiac device generally had a worse right heart systolic function than patients without one. However, all parameters did not show great alteration over time for both groups and thus this implies that the presence of an RV lead did not primarily worsen TV function. Including the findings additionally pertaining to LVEF, this study indicates that patients with a cardiac rhythm device were generally more ill from the onset than patients without a device.

The results in this study also suggest that the implantation of a PM or similar device decreased a patient's cumulative life expectancy.

4. 1. 1. Misleading Changes in TR Grading

The median TR grading in the PM group, which consisted of patients that had one of the three cardiac devices (PM, ICD, CRT) included in this study implanted, was significantly worse in the long-term follow-up, however it was to begin with as well. Additionally, the difference in medians was minimal in both periods. When looking at the changes within the PM group, the median long-term TR grade was calculated as significantly different, however the actual median number and IQR remained the same. This could be explained as that the distribution of grading changed over time, which can be observed in the pie charts 1 and in the bar graph 1. On the one hand, more patients' grading the PM group worsened than in the control, but on the other within the grand scheme no alteration in comparison to the initial TTE occurred.

Additionally, as seen in Figure 5 and 6, the way that patients' grading had changed by the end of this study did not reveal any further findings. There was no trend recognizable in both groups. It seems as though generally there was more shifting within the pacemaker group, but this instead made any generalizations less discernible. Furthermore, when directly comparing the bars for each group accordingly, it became clear that the final distributions were not divergent.

4. 1. 2. Direct Effects were not apparent

TR Vmax, PISA and vena contracta are all parameters that directly measure a value at the TV and its opening area. For all three of these in this study, there were no significant changes within the group observed, and only one minor difference regarding TR Vmax short-term. Even though TR Vmax was greater in the PM group, the only short-term significant difference was more likely due to statistical reasons, namely the small number of echocardiographies included in that time period. These findings imply that a RV lead did not impact direct parameters of TV function.

4. 1. 3. Indirect Effects were not apparent

In both the PM and control group, the RA volume and CVP revealed the same pattern. For both parameters, there was no change detectable within the groups, except that RA volume was significantly greater initially and CVP was significantly lower in the long-term examination in the control group. The RA volume determines RA pressure, thus also determines CVP[70]. If there were a true hemodynamic relevance, then both values would change more synchronously to each other.

The other parameters pertaining to right heart function in this study, such as the TAPSE or SPAP, do not show a worsened right heart function in either groups. This furthermore supports the assumption that the indirect TV parameters of a greater CVP and RA volume in the PM group were less likely due to an RV lead.

4. 1. 4. Baseline Characteristics could explain low LVEF

The PM group included significantly more patients with chronic renal insufficiency and the PM group had a significantly lower LVEF. One consideration is that a possible indication for implanting an ICD is low LVEF for primary prophylaxis, but patients who qualify for a secondary prophylactic implantation often have a low LVEF as well[37]. This would explain why the PM group had such a low LVEF in comparison to the control group. Additionally, the

characteristics chronic renal insufficiency and low LVEF in the PM group could correlate with each other regarding cardiorenal syndromes. Cardiorenal syndromes describe conditions, in which the low cardiac output over time has a negative effect on the renal function through several mechanisms, such as a constantly activated renin-angiotensin system and the production of natriuretic peptides[71]. It is not distinguishable, which organ is affected first, but it is a viable explanation for why these two characteristics were significant in the PM group.

In this study, LVEF was not affected by device implantation either. Alizadeh et al. conducted a study in 2011 with 115 patients who all had a normal LVEF at baseline. The study showed similar to this one that TR increased after PM implantation and that it did not have an effect on the left heart function[72].

4. 2. Comparison to Previous Studies

It is important to compare the findings in this study to the setting in current literature. There are several studies that concurred with the results of this study. A study conducted in 2009 by Klutstein et al. found that in patients with a PM and TR Grading of II or worse, the majority did not change in TR over time[73]. In 2012, Eleid et al. conducted a study in which TR was observed before and after the implantation of a cardiac device in patients with a bioprosthetic valve in comparison to a control group. Eleid et al. also found that the pacing leads did not have an effect on TR[74].

Furthermore, there are studies that demonstrated similar results pertaining to mortality, but they have to be compared critically due to different methodological procedures. Between 2002 and 2009, Höke et al. conducted a retrospective study at the Leiden University Medical Center and found that if an increase in TR Grading of over two classifications occurred, the long-term prognosis of a patient decreased. Contrary to this study, Höke et al. excluded patients who had received valve surgery or had HF and classified patients' TR Grade systematically based upon echocardiographic findings. These exclusions allowed a stronger correlational analysis. Höke at al. were able to show that a RV-Lead could have induced a strong decrease in tricuspid valve function and that the prognosis of a patient was negatively influenced by it[75].

There are also authors who contrarily suggested that the implantation of a cardiac device did have an effect on the TV. In 2014, Sadeddrini et al. conducted a retrospective study with 155 patients and found that the implantation of a cardiac device significantly worsened TR compared to patients who had received radiofrequency catheter ablation, but also that LVEF did not

significantly change and that the implantation with a CRT did not influence TR[76]. Arabi et al. conducted a prospective study similar to the current one in 2015. 41 patients with either a PM, ICD, or CRT had TTE examinations at one, six and 12 months after implantation. Arabi et al. found that TR increased significantly throughout all groups with a majority of 70.8% of all patients by at least one grade long-term. RV ejection fraction seemed to worsen after the implantation of a device. However, TR and general RV parameters showed no significant differences amongst different types of devices[77].

Furthermore, a study conducted by Kim et al. with 248 patients who had either a PM or ICD implanted showed that not only TR increased overall, but that the TR function worsened significantly more in patients with an ICD[63]. These results echo the observations made in this study.

In addition, reviews published by Al-Mohaissen in 2012 and Chang et al. in 2017 came to the same conclusion and stated that TR can be induced by cardiac device lead placement[78,79].

4. 3. Possible Mechanisms that induce Tricuspid Regurgitation

4. 3. 1. Mechanical Interference

There are several possible explanations as for why a patient could develop TR after the implantation of a cardiac device. One proposition is that the PM lead physically interferes with the TV leaflets in various ways. Saran et al. conducted a study in which 622 patients who had a PM, a TR of moderate to severe TR and had received TV surgery were examined retrospectively. The patients were divided into two groups: PM induced and PM associated TR. The first meaning that the PM lead had definitely caused TR by "restriction of the mobility of otherwise normal-appearing leaflets or subvalvular apparatus, scarring or fusion of leaflets to each other, leaflet adherence to the leads, leaflet perforation or chordal entrapment"[80]; the latter meaning it had not been directly caused by the lead. 42% of the patients had induced TR, 58% of the patients associated TR. The main cause for induced TR was restricted leaf mobility by the lead, the main cause for associated TR was functional TR[80]. Lin et al.[81] , Uehara et al.[82] and Mediratta et al.[83] are also examples of studies who found that TR Grading worsened after PM implantation due to lead intervention with the TV.

Saran et al. found that almost half the patients with a PM and a TR of minimum Grade II had a TR induced directly by the PM lead mainly due to leaflet obstruction, but overall functional TR

was more common[80]. This suggests that TR in paced patients is not obligatory, but if it does occur lead impediment is most likely the cause.

4. 3. 2. Exact Location of Leads

Some authors suggest that the exact placement of the lead within the TV or the specific leaflet affected by the lead plays a defining role. A case study published by Wardell et al. for example, identified the posterior leaflet as the most commonly affected leaflet causing TR[84]. Concerning the topography of the lead tip there are competing voices. For example, Wang et al. found that TR was observed more often if the lead tip was placed in the right ventricular outflow tract than in the right ventricular apex[85]. Krupa et al. conducted a study including 86 patients and did not discover a difference in TR between tip lead placement in the right ventricular outflow tract, apex or para-apex area[86]. It is debatable whether the lead tip and the leaflet affected are to be treated as independent, as the tip placement ultimately predetermines where the lead will trespass the TV.

4. 3. 3. Other Causes for TR

Various case studies have described other rare causes of TR after PM implantation, such as the PM lead perforating the papillary muscle[87], lead perforation of the TR Leaflets or chordae[82,88]

Not all complications are based on short-term effects. In an earlier paper by Becker et al. three case reports were published describing the “thrombotic encapsulation” of a PM lead after two weeks and the “fibrous encapsulation” of PM leads after eight and 12 months[89]. This implies that additional, more long-term effects, influence the TV function indirectly.

In 2010 the European Journal of Echocardiography published a study conducted by Vaturi et al. The study included 23 patients with a permanent pacemaker and a normal LVEF. The patients were divided into an active and non-active pacing group. Echocardiographic follow-ups were performed after the PM reprogramming. Although the study included few patients, Vaturi et al. found that the TR significantly worsened in the active pacing group indicating that the pacing settings were more influential than the actual presence of an RV lead[90].

Other considerable explanations pertain solely to the dynamics limited to the interaction between lead and valve directly. In 2017, Rydlewska et al. conducted a study in which the chest rays of patients who had undergone cardiac device implantation were examined. The objective of the study was to investigate whether radiological lead positioning identified in xrays could be

correlated to TR severity. Rydlewska et al. found that the following radiological signs of "insufficient lead length (…) or excessive lead length" correlated with a worse TR[91].

A study conducted by Celiker et al. in Japan examined echocardiographies of patients who had undergone PM implantation with either one or two leads placed. A significant increase in TR Grading was only observed in patients with two RV leads suggesting that the number of leads influences TV function[92].

4. 4. Is Echocardiography suitable for assessing TR?

Another important aspect of this study is whether transthoracic echocardiography is an efficient method of detecting or measuring lead induced TR. Even though 2D TTEs are a standard method of examining heart valves, there are authors that suggest otherwise. On the one hand, 2D TTE is a useful, safe and an easily ready method for examining mechanical complications between PM leads and the TV. However, 3D echocardiography or TEE allow a much more detailed observation of the lead route within the heart[93]. A great benefit of using real time 3D echocardiography pertaining to TR is being able to view all three leaflets moving at once during a cardiac cycle[94]. A publication by Wardell et al. emphasized that echocardiography alone was not sufficient, or rather it had not delivered secure evidence in their study as to whether the lead itself was the direct cause of TR[84]. The publication suggested that if patients develop a worse TR after implantation, and no other left heart cardiac pathologies explain the symptoms, a lead induced TR was likely but could not be identified immediately via echocardiography[84].

Muraru et al. also emphasized the limitations of 2D echocardiography and suggest the use of 3D to be superior[95]. The authors reasoned as following: not all three leaflets are routinely visualized, "the maximal dimensions and spatial configuration of the oval, saddle-shaped tricuspid annulus cannot be precisely and reproducibly quantified by a single linear measure, (…) and TV leaflet commissures, coaptation orifice, and/or valve area planimetry are generally impossible to assess by 2DE, either from transthoracic or transesophageal approach, because an en face view of the entire valve is required (…)" [95]. Murarau et al. mainly criticized that 2D echocardiography enables less detailed imaging.

In a nutshell, 3D echocardiography is preferable if available. In clinical practice however, 2D echocardiography is usually more accessible. 2D echocardiography can be used to examine TR with limitations concerning the degree of visualization.

4. 5. Baseline Differences

The observed baseline data in table 6 shows that the PM group and the control group were similar. Therefore, statistical and interpretational comparisons were justifiable. The control group, who did not have a cardiac device implanted, had significantly more coronary stents implanted and suffered more from arterial hypertension. It is disputable whether these characteristics were reasons for which patients in the control were not operated within the context of receiving a PM or whether these characteristics were the aftermath of not having a device.

4. 6. Possible Reasons for decreased Cumulative Survival

As shown in figure 3, the patients in the PM group had a lower estimated probability of cumulative survival. It is not distinguishable which reason was mainly responsible for this. The PM group had an unaffected LVEF, however Thackrey et al. examined HF in paced patients and found that left ventricular dysfunction was in fact common in patients with a PM, however actual HF was only diagnosed after implantation and more often in patients with a single chamber PM[96]. If PM leads do not seem to have an effect on LVEF, then the presence of a PM must have another effect in the right heart function correlating to HF, as suggested in this study.

Also, the main indications for a PM are arrhythmias. Specific arrhythmias are life-shortening conditions at the outset and thus patients suffering from arrhythmia already have a possible lower life expectancy than patients without arrhythmia[97]. Patients who receive an ICD are generally at a higher risk of sudden cardiac death- this is why they receive an ICD in the first place[37].

Furthermore, patients who have received a cardiac device were operated and hence are at risk of general post-operative complications such as infections or embolisms, which can cause death.

4. 8. Limitations

There were several limitations in this study. First of all, data collection in a retrospective study is finite. If certain information about exams and patients was missing, it was not possible to attain it at a later date. This resulted in some exams having to be excluded from the study because of incomplete documentation.

Further limitations relate to the study population. The number of patients was not very large but was comparable to prior studies. Patients were selected and the control group was not assigned randomly. Also, the patients' main diagnoses as to why consecutive TTE examinations were performed in the first place or why patients in the PM had received a cardiac device were not regarded. This led to the comparison of patients who had different underlying illnesses, even though patients were matched based on mutual characteristics.

Additionally, a limitation pertaining to the echocardiographies was the inter observer variability[98]. The TTE examiners were fully qualified and experienced, but subjectivity to a certain degree could not be eliminated. Also, the higher the grading, the easier it is or moreover the more likely it is to measure echocardiographic parameters accurately and reliably[56]. In this study the majority of patients had lower TR gradings. This made measuring specific values in the TTEs more difficult.

Lastly, there are limitations referring to the statistics applied in this study. TR Grading was an ordinal scaled variable. This did not allow the calculation of an actual mean. Moreover, not all variables were truly normally distributed. These criteria meant that certain mathematical approaches were not legitimized and confined statistical assertions.

4. 9. Conclusion and Outlook

This study revealed that an RV lead does not have an actual, real impact on the TV function. Current literature seemed to be more in agreement on a lead having an effect, however the harder evidence found in this study rationally provides evidence for the opposite.

If the implantation of a cardiac device did in fact induce worse TV function, this study shows that it would be more likely due to accompanying illnesses or due to the primary indication patients have for receiving a cardiac device in the first place. Contrarily in common literature physical lead interference with the TV leaflets was a widely accepted explanation. It still remains unclear whether or to what extent other factors might impact TV function, such as the exact lead placement within the ventricle, which leaflet is mostly affected, or whether the number of leads per device are relevant.

This study helps identify which clinical factors or echocardiographic values remain uninfluenced by a RV lead. It revealed that left and right heart function were independent from cardiac device

implantation. It must however be differentiated between a low LVEF and actual symptomatic HF.

This study also provided stronger evidence, that patients with a cardiac device have a greater mortality. However, it remains unclear as to whether this effect was due to the devices themselves or on external factors and accompanying diseases.

Taking into consideration that intracardial leads could be a cause of TR, new types of PM implantations are being discussed, such as extracardiac leads or even leadless PMs. It seems reasonable to implement such new methods. A recent study conducted by Salaun et al. supports this proposition. They examined 23 patients with leadless PMs and found that there was no significant change in right ventricular and tricuspid valve paremeters[99]. Another benefit of epicardial leads is that they can be placed as necessary independent of anatomical coronary or cardiac difficulties or obstructions[100]. Meanwhile, leadless PMs are being implanted more regularly and technology has improved greatly. Subcutaneous defibrillators or injectable loop recorders, which function as small subcutaneous ECGs, are further examples of technological developments towards the direction of extracardiac devices[101].

Additional research is needed in order to differentiate the increased mortality in patients with a cardiac device. The research questions of this study need to be investigated by further studies with a greater study population and more exact imaging techniques in order to discriminate between morphological and indirect parameters. If procedural changes regarding cardiac device implantation occur within the scope of the technological advancements, they could affect a large patient population in Germany.

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Eidesstattlichliche Erklärung

„Ich, Emily Roczek, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Influence of Right Ventricular Leads of Cardiac Devices on Tricuspid Valve Function and Occurrence of Tricuspid Regurgitation selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Tabellarischer Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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