Permanent Pacemaker Implantation After Tricuspid Valve Repair Surgery

Alyssa Morrison

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PERMANENT PACEMAKER IMPLANTATION
AFTER TRICUSPID VALVE REPAIR SURGERY

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

By
Alyssa Rae Morrison
Class of 2024
ABSTRACT

PERMANENT PACEMAKER IMPLANTATION AFTER TRICUSPID VALVE REPAIR
SURGERY

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(Sponsored by Sarwat Chaudhry, Department of Internal Medicine, Yale School of Medicine, New Haven, CT)

Recent studies suggest that permanent pacemaker implantation after tricuspid valve repair may be more common than previously thought. Our primary aim was to assess the rates of early (within 30 days of surgery) and late (more than 30 days after surgery) permanent pacemaker implantation (PPI) after tricuspid valve repair (TVr) surgery. Our secondary aims included exploring risk factors for PPI after TVr and assessing outcomes.

We performed a retrospective analysis of 231 isolated and concomitant tricuspid valve repairs for primary and secondary tricuspid valve regurgitation at a single quaternary academic center performed from 2014–2022.

Early pacemaker implantation was performed in 10.0% of patients (n=23) at median 6 (interquartile range [IQR], 5–7) days after surgery, with a range of 2–14 days. In assessing differences between patients with early pacemaker implantation and those without, there were no significant differences between the groups regarding baseline demographic characteristics, comorbidities, or operative characteristics. The indications
for the pacemakers were atrioventricular node block in 69.6% and sinoatrial node
dysfunction in 30.4%. Median follow-up was 2.8 (IQR, 1.2–4.8) years. Late pacemaker
implantation, more than 30 days after surgery, occurred in 15 patients (7.2%), median 1.2
(IQR, 0.6–4.6) years after tricuspid valve repair. Although these analyses were under-
powered, we found that the patient and surgical factors we evaluated, including history of
atrial fibrillation and MAZE procedure, were not significant predictors of PPI. There was
no significant difference in the long-term survival based on early pacemaker implantation
status (unadjusted hazard ratio 0.54, 95% CI 0.22–1.37, $P=0.305$) or late pacemaker
implantation (unadjusted hazard ratio 0.79, 95% CI 0.19–2.18, $P=0.695$).

The rate of permanent pacemaker implantation following tricuspid valve repair
within 30 days postoperatively in our cohort was 10.0%, suggesting pacemaker
implantation is not an uncommon occurrence in the perioperative period, and typically
occurs within the first 10 days. Atrioventricular block accounts for the majority of early
pacemakers (69.6%), followed by sinoatrial node dysfunction (30.4%).
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Arnar Geirsson for his support and mentorship throughout my time in medical school—he has helped me grow as a researcher and a clinician. I would also like to thank the Yale Cardiac Surgery Outcomes Research Group and the mentors and colleagues who helped this project come to life.

I am so grateful to Yale School of Medicine, especially the Office of Student Research, for providing opportunities for me to explore and grow during my time in medical school. This work was funded through the Office of Student Research, the National Heart, Lung, and Blood Institute, and the Richard K Gershon, MD Endowment for Medical Student Research. I would like to say a special thank you to Dr. Sarwat Chaudhry for graciously supporting me in this thesis process.

I would also like to thank my friends and family for their unwavering support throughout medical school and everything leading up to this point, I could not have done this without you.
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INTRODUCTION

Tricuspid Valve Disease

The heart contains four valves—the mitral, tricuspid, aortic, and pulmonic. The tricuspid valve connects the right atrium to the right ventricle of the heart and is a tri-leaflet valve. Right-sided heart disease and the tricuspid valve have historically not been a priority in cardiology and cardiac surgery, with the tricuspid valve nicknamed “the forgotten valve”. Over time, our understanding of right-sided heart disease and the importance of the tricuspid valve have improved, and in recent years there has been new interest in addressing tricuspid valve disease.

Tricuspid regurgitation (TR) is the most common form of tricuspid valve disease and trace TR and above may be detectable in over 80% of the population. TR can be either primary or secondary in regards to its origin, with secondary being far more common. Primary TR refers to an intrinsic problem with the tricuspid valve which can be congenital or acquired, including as a result of rhematic heart disease, as a complication of an implantable device such as a pacing wire, infective endocarditis, or damage from therapeutic radiation to the chest. In cases of primary TR, the damage can occur to the leaflets, chordae tendinea, or papillary muscles.

Secondary TR accounts for over 80% of TR and is most often the result of left-sided valvular disease or pulmonary hypertension. Other causes of secondary TR include atrial fibrillation and chronic right ventricular pacing. This type of TR is sometimes referred to as “functional tricuspid regurgitation” and is not a problem that originated with the valve.
itself but rather occurs as a result of right ventricular remodeling that leads to annular
dilation and decreased coaptation of the valve, resulting in regurgitation through the
tricuspid valve.

The tricuspid valve is the most anterior valve of the heart and connects the right atrium
and right ventricle. The annulus of the tricuspid valve is elliptical in shape with three
leaflets—anterior leaflet, posterior leaflet, and septal leaflet (Figure 1). The tricuspid
valve has three papillary muscles that support the valve and are connected to the leaflets
by chordae tendineae. Of note, the tricuspid valve, particularly the septal leaflet, is
located near the atrioventricular (AV) node and the Bundle of His, essential components
of the electrical conduction system of the heart (Figure 2).
Chronic tricuspid regurgitation is often asymptomatic, but over time can contribute to right-sided heart failure that can be symptomatic. Additionally, if TR is associated with conditions such as pulmonary hypertension or left-sided heart disease, symptoms related to the primary condition are likely to precede TR symptoms and be more pronounced.\textsuperscript{4} There is typically a period of right ventricular compensation followed by further remodeling and decompensation that can lead to chronic right heart failure.\textsuperscript{5} TR is most commonly identified as part of comprehensive evaluation of a different primary disease, such as mitral valve disease or pulmonary hypertension. The gold standard of diagnosis is an echocardiogram, typically, transthoracic, which allows for grading of the regurgitation. TR is traditionally graded as mild, moderate, or severe, with some considering grades above severe, such as massive.\textsuperscript{6} TR often presents with a holosystolic murmur that may be identified on physical exam, and if advanced, symptoms such as dyspnea on exertion or volume overload may lead to diagnostic evaluation that demonstrates TR.

The presence and severity of tricuspid regurgitation has major implications for morbidity and mortality. A large retrospective study through the Veterans Administration system demonstrated a clear relationship between increasing severity of TR and death, even when controlling for factor such as ejection fraction and pulmonary artery pressure.\textsuperscript{7} Another study of isolated TR again found that TR is an independent predictor of morbidity and mortality.\textsuperscript{8} These studies, among others with similar conclusions, support the growing body of evidence that tricuspid regurgitation is not a benign condition, including in the setting of concomitant left-sided heart disease such as left-sided heart
failure and mitral valve disease.\textsuperscript{9,10} Severe TR can contribute to renal failure and liver failure as well as worsening overall cardiac function.\textsuperscript{11}

\textit{Surgery and Treatment of Tricuspid Valve Disease}

Once the risk associated with tricuspid valve regurgitation has been identified, the question becomes—what can and should be done about it? In the case of both primary and secondary TR, patients should be medically optimized. Medications for TR are limited, typically involving diuretics to manage volume status and possibly medications to address the underlying cause of the TR, both of which are class 2a recommendations.\textsuperscript{11} Treatments of the underlying cause may include treatment of pulmonary hypertension or rhythm control in the case of atrial fibrillation. Along with medical management, it is important to monitor for progression of TR as well as development of right heart failure and any worsening of symptoms.

Surgical repair of the tricuspid valve is the mainstay for definitive treatment of tricuspid regurgitation, in both primary and secondary TR. The indications for surgical treatment of tricuspid regurgitation by the American Heart Association and the American College of Cardiology are listed in Table 1.\textsuperscript{11}
### Table 1: Recommendations for Surgical Tricuspid Valve Repair

<table>
<thead>
<tr>
<th>Class of Recommendation</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In patients with severe TR undergoing left sided valve surgery, tricuspid valve surgery is recommended</td>
</tr>
<tr>
<td>2a</td>
<td>In patients with progressive TR undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either 1) tricuspid annular dilation (tricuspid annulus end diastolic diameter &gt;4.0 cm) or 2) prior signs and symptoms of right-sided HF</td>
</tr>
<tr>
<td>2a</td>
<td>In patients with signs and symptoms of right-sided HF and severe primary TR, isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations</td>
</tr>
<tr>
<td>2a</td>
<td>In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy, isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations</td>
</tr>
<tr>
<td>2b</td>
<td>In asymptomatic patients with severe primary TR (Stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered</td>
</tr>
</tbody>
</table>
In patients with signs and symptoms of right-sided HF and severe TR (Stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction.

Surgery of the tricuspid valve is most commonly performed using open sternotomy but can be done minimally invasively through right thoracotomy or robotic approach and is performed using cardiopulmonary bypass in all instances. Tricuspid valve surgery typically involves either a repair of the native valve or replacement of the native valve with an artificial valve, which can be either biologic or prosthetic. Tricuspid valve repair is more common and preferred when possible, but replacement is sometimes necessary when repair is not feasible.\textsuperscript{1,12} The most common repair technique for the tricuspid valve is the placement of an annuloplasty, typically either a band or ring sutured into the annulus. This reinforces both the size and shape, which are frequently distorted in secondary tricuspid regurgitation.\textsuperscript{13} In addition to valve annuloplasty, valve repair techniques may include placement of sutures at the commissures to improve coaptation or placement of neochords in the case of flail leaflets.\textsuperscript{1,13}

Isolated tricuspid valve repair remains a surgery with a high rate of morbidity and mortality, although it only account for about 15% of all tricuspid valve repairs.\textsuperscript{14} The mortality rate is about 8-10% without significant improvements in the last 20 years.\textsuperscript{15-18}
These patients often present with advanced disease given the indolent course of isolated TR and are high-risk surgical candidates. Morbidity rates approach 50% and many patients have a prolonged recovery.\textsuperscript{16}

In addition to traditional surgical repair and replacement of the tricuspid valve, there are increasing options for minimally invasive treatments for TR, such as transcatheter approaches.\textsuperscript{19} The recently published TRILUMINATE trial of transcatheter edge-to-edge repair among patients that were not surgical candidates demonstrated significant improvement in the composite primary endpoint that included quality of life, avoidance of tricuspid valve surgery, death, and hospitalizations.\textsuperscript{20} This is an evolving area of innovation and we will likely see increased utilization of transcatheter tricuspid valve procedures moving forward.

In the past, the prevailing surgical approach to secondary TR was to repair the primary problem and not intervene upon the tricuspid valve.\textsuperscript{21} The rationale was that by addressing the underlying cause, such as surgical treatment of mitral valve prolapse, the TR would improve or resolve entirely, thereby not requiring further intervention on the tricuspid valve. While it is true that TR often improves after surgically correcting left sided valvular disease, studies have also demonstrated that the TR often remained clinically significant even after primary surgical repair of left sided valvular disease and may necessitate further surgical intervention.\textsuperscript{22,23}
There has been increased interest in performing tricuspid valve repair at the same time as left sided valve surgery, even if the patient does not meet the class 1 recommendation of severe TR at the time of surgery. Several clinical trials have been conducted in recent years to further investigate the potential benefits of concomitant tricuspid valve repair. In the Gammie et al CTSNet trial, patients undergoing mitral valve surgery with moderate TR or less-than-moderate TR with annular dilation were randomized to also undergo tricuspid valve repair or not. Benefits of tricuspid valve annuloplasty in the management of secondary tricuspid valve regurgitation were demonstrated, but they also demonstrated an increased need for permanent pacemaker with tricuspid valve repair compared to mitral valve surgery alone. Within 30 days of surgery, 11.6% of patients with concomitant mitral and tricuspid valve surgery required permanent pacemaker implantation and a cumulative 14.1% of patients required permanent pacemaker implantation over the course of the two-year follow up period. This ignited a conversation around permanent pacemaker implantation following tricuspid valve surgery.

Cardiac surgery outcomes reporting has historically focused on 30-day outcomes. In the 1980’s there was a push for comprehensive surgical outcomes reporting, including morbidity and mortality, to allow for evaluation of surgeons, hospitals, and systems. Much of this reporting began within the Veterans Administration system, conducted by the American College of Surgeons, which allowed for not only assessment out outcomes but also risk adjustment based on patient-level factors. They focused on not only on outcomes within the index admission, but also 30-day outcomes that captured
readmissions. This was later expanded into the National Surgical Quality Improvement Program. This format has established the basis for much of surgical outcomes reporting in the last two decades and many other societies have followed suit, including the Society of Thoracic Surgeons (STS). STS also established a database to track and analyze outcomes, including morbidity and mortality, in 1989, pulling data from the majority of cardiac surgery centers in the United States. The STS database of adult cardiac surgery outcomes emphasizes 30-day outcomes that are widely used in cardiac surgery. As a result, the convention for reporting complications, such as permanent pacemaker implantation, tends to be 30-day outcomes reporting. In addition to society-driven database reporting, multiple states also instituted public reporting of cardiac surgery outcomes. More recently there has been a push to expand data collection to 90 days postoperatively and even beyond, including within the STS database, but this data is not as widely available as 30-day outcomes and is often reported separately.

Permanent Pacemakers after Valve Surgery

Injury to the electrical conduction system of the heart and need for permanent pacemaker implantation (PPI) is a known complication of cardiac surgery, particularly with atrioventricular valve surgery, as much of the conduction system is located within the intraventricular septum. It has been generally accepted to be a rare complication for most valve procedures, including tricuspid valve repair (TVr), with rates of about 2-6%, although rates as high as 27% have been reported following tricuspid valve repair and replacement.
Understanding the risk of permanent pacemaker implantation requirement after tricuspid valve surgery is important for surgical planning and decision making for both the patient and the surgeon, particularly as the recommendations for tricuspid valve repair are expanding. Permanent pacemakers are an excellent tool for treating serious electrical conduction disorders, including in the perioperative period, but they come with associated risks including increased risk of infection, thrombosis, and long-term side effects such as pacemaker induced cardiomyopathy. The objective of this study was to determine the rate of both early (within 30 days of surgery) and late (more than 30 days after surgery) permanent pacemaker implantation following tricuspid valve repair surgery at a quaternary academic center.
The primary aim of this study was to evaluate the rate of early permanent pacemaker implantation, within 30 days of surgery, and late pacemaker implantation, more than 30 days after surgery, among patients undergoing isolated or concomitant tricuspid valve repair surgery at Yale New Haven Hospital between 2014 and 2022 for primary or secondary tricuspid regurgitation.

Secondary aims included evaluating:

- Differences in patient characteristics amongst those with and without early pacemaker implantation
- Exploratory analysis of predictors of early pacemaker implantation
- Late permanent pacemaker implantation (more than 30 days after surgery) rate
- Timing of both early and late pacemaker implantation
- Survival analysis for those with and without early pacemaker implantation
- All-cause mortality within 30 days and during the entire follow-up period
METHODS

Student contributions

Under the supervision and guidance of Arnar Geirsson, MD, the student, Alyssa Morrison, contributed to each step of the research process and preparation of this thesis.

Contributions to this work are outlined below:

- Alyssa Morrison, BS—Formulation of study, retrospective data collection, statistical analysis, drafting of manuscript, and critical revision
- Sigurdur Ragnarsson, MD—Formulation of study, statistical advising, critical revision
- Andrea Amabile, MD—Critical revision
- Makoto Mori, MD—Critical revision
- Markus Krane, MD—Formulation of study, critical revision
- Arnar Geirsson, MD—Formulation of study, critical revision

Ethics statement

This study was approved by the Yale Institutional Review Board (IRB) prior to initiation of the study, under IRB No. 2000020356. The study was conducted in an ethical manner accordance with the ethical guidelines set out by the Yale University IRB.
Informed consent was waived by the Yale University IRB as this was a retrospective study using de-identified data that posed minimal risk to study participants.

Study Design

We performed a single-center, retrospective cohort study. Information was gathered for all consecutive tricuspid valve procedures performed at Yale New Haven Hospital from 2014–2022. Both isolated TVr procedures and those with concomitant procedures were included.

Procedures excluded from study (Figure 3):

- Tricuspid valve replacements ($n=84$)
  - Tricuspid valve replacement surgery known to be higher risk than mitral valve repair surgery. Specifically, they are associated with greater morbidity and mortality including higher rates of permanent pacemaker implantation.$^{35,36}$

- Tricuspid valvectomies ($n=10$)
  - Valvectomies are most often performed in cases of infective endocarditis and are typically followed by a later tricuspid valve replacement, which are excluded from this study.$^{37}$ Valvectomies do not typically include an annuloplasty or other type of sutures into the annulus that typically increase the risk of pacemaker requirement.

- Tricuspid valve mass removals that did not involve a valve repair ($n=1$)
Tricuspid valve repairs due to injury from ventricular assist devices ($n=10$)

Patients excluded from study:

- Patients with pre-existing permanent pacemakers or automatic implantable cardioverter defibrillators (AICDs) ($n=53$)
- Patients with permanent pacemakers that were placed during the index operation ($n=4$)

Concomitant procedures performed included:

- Mitral valve repair or replacement
- MAZE procedure
- Aortic valve replacement
- Left atrial appendage exclusion
- Coronary artery bypass graft

Patient demographics, perioperative, and follow up data were collected from the Yale New Haven Hospital electronic health record system and institutional Society of Thoracic Surgeons (STS) database. We utilized the health information exchange tool through the electronic health record to obtain medical records, including pacemaker implantation, from outside institution(s) participating in this exchange tool.

Early pacemaker implantation is defined as permanent pacemaker implantation within 30 days of the index tricuspid valve repair surgery. Late pacemaker implantation is defined
as any permanent pacemaker implantation that occurs more than 30 days after the index tricuspid valve repair surgery.

Statistical Methods

Normally distributed, continuous variables (as determined by the Kolmogorov-Smirnov test), were expressed as mean ± standard deviation and compared using a student’s t test. Non-normally distributed, continuous variables were expressed as median (Interquartile Range [IQR]) and compared using the Mann-Whitney test. Categorical variables were expressed as absolute and relative frequencies and compared using the Fisher’s exact test or χ² test. Simple univariate and multivariate logistic regressions were performed to assess association. Kaplan-Meier analysis was used to assess survival.

We performed a post-hoc power calculation to assess the ability of this study to detect a significant association between independent variables and early pacemaker implantation. The analysis was performed for a sample of four variables that have been demonstrated to be significantly associated with permanent pacemaker implantation following valvular surgery in the literature—history of myocardial infarction, history of atrial fibrillation, MAZE procedure, and concomitant mitral valve surgery. Each of the factors demonstrated insufficient power to detect a significant association in this study for early pacemaker implantation (Table 2). The decision was made to include these analyses as exploratory. We opted not to perform multivariate regression given these power limitations.
Table 2. Post-Hoc Power Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number with characteristic</th>
<th>Number w/o characteristic</th>
<th>PPI with characteristic</th>
<th>PPI without characteristic</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of MI</td>
<td>39</td>
<td>192</td>
<td>17.9% (7/39)</td>
<td>8.3% (16/192)</td>
<td>45.7</td>
</tr>
<tr>
<td>History of afib</td>
<td>143</td>
<td>88</td>
<td>12.6% (18/143)</td>
<td>5.7% (5/88)</td>
<td>38.8</td>
</tr>
<tr>
<td>MAZE procedure</td>
<td>57</td>
<td>174</td>
<td>15.8% (9/57)</td>
<td>8% (14/174)</td>
<td>41.4</td>
</tr>
<tr>
<td>Mitral surgery</td>
<td>190</td>
<td>41</td>
<td>11.1% (21/190)</td>
<td>4.9% (2/41)</td>
<td>16.7</td>
</tr>
</tbody>
</table>

PPI, permanent pacemaker implantation; MI, myocardial infarction; afib, atrial fibrillation

Statistical analysis was performed with GraphPad Prism (Version 9.5.0, GraphPad Software, San Diego, California). Statistical significance was set at a two-sided P value ≤ .05.
RESULTS

Baseline and Preoperative Characteristics

The final cohort for this study included 231 patients who underwent a tricuspid valve repair surgery. The median age at the time of surgery was 70 (IQR 58-78) years of age and 52.4% were female (Table 3). The cohort presented with a variety of pathologies, including primary and secondary tricuspid valve disease; 8.6% of cases were for active infective endocarditis. Twenty-three patients required permanent pacemaker implantation within 30 days of the index operation (10.0%). When comparing baseline characteristics of those who did or did not have permanent pacemaker implantation within 30 days of surgery, there were no significant differences in age, sex, history of myocardial infarction (MI), left ventricular ejection fraction (EF), history of atrial fibrillation, or rates of prior cardiac surgery between the two groups. The rate of active infective endocarditis was 4.3% amongst those with early permanent pacemaker implantation and 9.1% amongst those without early permanent pacemaker implantation (P=0.702).
Table 3. Baseline Characteristics Amongst those with and without Early Pacemaker after Tricuspid Valve Repair

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n=231)</th>
<th>Early Pacemaker (n=23)</th>
<th>No early Pacemaker (n=208)</th>
<th>Late Pacemaker (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>70 (58-78)</td>
<td>74 (63-80)</td>
<td>70 (58-77)</td>
<td>76 (70-82)</td>
</tr>
<tr>
<td>Female sex</td>
<td>121 (52.4)</td>
<td>11 (47.8)</td>
<td>110 (52.9)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>History of MI</td>
<td>39 (16.9)</td>
<td>7 (30.4)</td>
<td>32 (15.4)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Left ventricular EF, %</td>
<td>58 (53-63)</td>
<td>60 (57-63)</td>
<td>58 (53-63)</td>
<td>58 (53-63)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>184 (79.7)</td>
<td>20 (87.0)</td>
<td>164 (78.8)</td>
<td>14 (93.3)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>143 (61.9)</td>
<td>18 (78.2)</td>
<td>125 (60.1)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>History of cardiac surgery</td>
<td>37 (16.0)</td>
<td>2 (8.7)</td>
<td>35 (16.8)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Active IE</td>
<td>20 (8.6)</td>
<td>1 (4.3)</td>
<td>19 (9.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range) or n (%). MI, myocardial infarction; EF, ejection fraction; IE, infective endocarditis

Operative Characteristics

There were no significant differences in the cardiopulmonary bypass time or aortic cross clamp time amongst those with and without early permanent pacemaker implantation (Table 4). Sternotomy, thoracotomy, and robotic–assisted approaches were used at similar rates amongst the two groups.
Many patients had concomitant procedures, with the most common being mitral valve surgery (35.1% mitral valve repair, 47.2% mitral valve replacement), MAZE procedure (24.7%), and aortic valve replacement (17.7%) without significant differences between those with and without early permanent pacemaker implantation. The size of the tricuspid valve annuloplasty ring/band, mitral valve annuloplasty ring/band, and prosthetic mitral valve were not significantly different between the two groups. Prosthetic valve/annuloplasty size was not associated with increased risk of permanent pacemaker implantation. The rate of MAZE procedure was 23.1% amongst those without early permanent pacemaker implantation and 39.1% amongst those with permanent pacemaker implantation, but the difference was not significant (P=0.123).
Table 4. Operative Characteristics Amongst those with and without Early Pacemaker after Tricuspid Valve Repair

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n=231)</th>
<th>Early Pacemaker (n=23)</th>
<th>No early Pacemaker (n=208)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operative Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td>138 (109-168)</td>
<td>134 (113-164)</td>
<td>140 (108-169)</td>
<td>0.859</td>
</tr>
<tr>
<td>Aortic cross clamp time, minutes</td>
<td>101 (78-126)</td>
<td>103 (87-111)</td>
<td>101 (78-126)</td>
<td>0.952</td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
<td></td>
<td></td>
<td>0.429</td>
</tr>
<tr>
<td>- Midline sternotomy</td>
<td>178 (77.1)</td>
<td>16 (69.6)</td>
<td>162 (77.9)</td>
<td></td>
</tr>
<tr>
<td>- Thoracotomy</td>
<td>16 (6.9)</td>
<td>3 (13.0)</td>
<td>13 (6.25)</td>
<td></td>
</tr>
<tr>
<td>- Robotic assisted</td>
<td>36 (15.6)</td>
<td>3 (13.0)</td>
<td>33 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>190 (82.3)</td>
<td>21 (91.3)</td>
<td>169 (81.3)</td>
<td>0.386</td>
</tr>
<tr>
<td>Mitral annuloplasty size, mm</td>
<td>26 (5), 28(10),</td>
<td>26 (0), 28 (1),</td>
<td>26 (5), 28 (9),</td>
<td>0.117</td>
</tr>
<tr>
<td></td>
<td>30 (17), 32(16),</td>
<td>30 (0), 32 (1),</td>
<td>30 (17), 32 (15),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (15), 36(11),</td>
<td>34 (1), 36 (2),</td>
<td>34 (14), 36 (9),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38 (2)</td>
<td>38 (1)</td>
<td>38 (1)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve replacement size, mm</td>
<td>25 (5), 27 (25),</td>
<td>25 (0), 27 (3),</td>
<td>25 (5), 27 (22),</td>
<td>0.368</td>
</tr>
<tr>
<td></td>
<td>29 (45), 31 (20),</td>
<td>29 (6), 31 (1),</td>
<td>29 (39), 31 (19),</td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 (14)</td>
<td>33 (4)</td>
<td>33 (10)</td>
<td></td>
</tr>
<tr>
<td>Tricuspid annuloplasty size, mm</td>
<td>26 (58), 28 (64),</td>
<td>26 (5), 28 (6),</td>
<td>26 (53), 28 (58)</td>
<td>0.459</td>
</tr>
<tr>
<td></td>
<td>30 (62), 32 (19),</td>
<td>30 (8), 32 (2)</td>
<td>30 (54), 32 (17)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34 (11), 36 (4)</td>
<td>34 (2), 36 (0)</td>
<td>34 (9), 36 (4)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>31 (13.4)</td>
<td>3 (13.0)</td>
<td>28 (13.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>MAZE procedure</td>
<td>57 (24.7)</td>
<td>9 (39.1)</td>
<td>48 (23.1)</td>
<td>0.123</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>41 (17.7)</td>
<td>3 (13.0)</td>
<td>38 (18.3)</td>
<td>0.774</td>
</tr>
</tbody>
</table>

Values are expressed as median (interquartile range) or n (%).
Within 30 days postoperatively, 10.0% (23/231) patients required permanent pacemaker implantation or combined permanent pacemaker/automatic implantable cardioverter defibrillator (AICD). Permanent pacemaker implantation occurred at median 6 (IQR 5–7) days postoperatively with a range of 2-14 days (Figure 4). The indications for the permanent pacemakers were complete or high-grade atrioventricular (AV) node block in 69.6% of patients and sinoatrial (SA) node dysfunction in 30.4% of patients. Of the 7/23 patients who had permanent pacemaker implantation for SA node dysfunction, 100% had history of atrial fibrillation prior to surgery. None of the 7 early SA node dysfunction patients had history of sick sinus syndrome prior to surgery and 4/7 underwent a concomitant MAZE procedure for atrial fibrillation at the time of surgery. Of the permanent pacemakers implanted within 30 days, two were combined pacemaker/AICD because the patients also met criteria for primary prevention of sudden cardiac death related to their pre-existing heart failure with reduced ejection fraction. The majority of patients with pacemaker implantation were dual chamber paced (82.6%) and 17.4% of patients were ventricularly paced. The 30-day mortality rate was 5.2% in this cohort in which 16.0% were redo operations. There were no 30-day mortalities amongst patients with early permanent pacemaker implantation (P=0.617).

We performed an exploratory univariate regression analysis to evaluate for predictors of permanent pacemaker implantation and the results can be found in Table 5. None of the independent variables reached significance at the level of P<0.05. Prior myocardial infarction approached significance (odds ratio 2.41, 95% CI 0.87—6.13, P=0.074) as
well as MAZE procedure which had an odds ratio of 2.14 (95% CI 0.85—5.20, \( P=0.096 \)). Factors that did not approach or reach significance included sex, hypertension, redo status of the operation, left ventricular ejection fraction, and size of tricuspid annuloplasty.

**Table 5.** Predictors of permanent pacemaker implantation within 30 days of index operation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03</td>
<td>1.00—1.08</td>
<td>0.072</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.22</td>
<td>0.51—2.94</td>
<td>0.645</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>2.41</td>
<td>0.87—6.13</td>
<td>0.074</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.71</td>
<td>0.65—5.36</td>
<td>0.289</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>1.02</td>
<td>0.98—1.08</td>
<td>0.341</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.33</td>
<td>0.89—7.29</td>
<td>0.107</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.79</td>
<td>0.58—7.83</td>
<td>0.365</td>
</tr>
<tr>
<td>Redo status</td>
<td>0.47</td>
<td>0.07—1.71</td>
<td>0.323</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>0.37</td>
<td>0.02—1.88</td>
<td>0.336</td>
</tr>
<tr>
<td>Mitral surgery</td>
<td>2.42</td>
<td>0.67—15.5</td>
<td>0.245</td>
</tr>
<tr>
<td>Size of mitral annuloplasty/prosthetic valve</td>
<td>1.12</td>
<td>0.95—1.31</td>
<td>0.170</td>
</tr>
<tr>
<td>Size of tricuspid annuloplasty</td>
<td>0.99</td>
<td>0.87—1.04</td>
<td>0.806</td>
</tr>
<tr>
<td>Aortic valve replacement</td>
<td>0.67</td>
<td>0.15—2.09</td>
<td>0.536</td>
</tr>
<tr>
<td>MAZE procedure</td>
<td>2.14</td>
<td>0.85—5.20</td>
<td>0.096</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Late Outcomes

Median follow up was 30.3 months (IQR 11.9-55.4 months) after surgery. There was no significant difference in patient survival based on early permanent pacemaker implantation (Figure 5) (hazard ratio 0.55, 95% CI 0.22–1.37, P=0.305). After the 30-day period, an additional 7.2% (n=15) of patients went on to require permanent pacemaker implantation during follow up (Table 6). Late permanent pacemaker implantation occurred at median 1.2 years (IQR 0.6 – 4.6) after TVr. The rate of permanent pacemaker implantation within 2 years of TVr, including both early and late permanent pacemaker implantation, was 14.3%. Indications for late permanent pacemaker implantation include complete or high-grade AV node block (26.7%), SA node dysfunction (66.7%), and unknown (6.7%). Of the patients with late permanent pacemaker implantation, 39.1% had a MAZE procedure during the index operation. Late permanent pacemaker implantation was not associated with an increased risk of death (unadjusted hazard ratio 0.79, 95% CI 0.19-2.18, P=0.695). During the follow up period, only one patient required reoperation, which was due to recurrent infective endocarditis.
Table 6. Outcomes Amongst those with and without Early Pacemaker after Tricuspid Valve Repair

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole cohort (n=231)</th>
<th>Early Pacemaker (n=23)</th>
<th>No early Pacemaker (n=208)</th>
<th>P value</th>
<th>Late Pacemaker (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>12 (5.2)</td>
<td>0 (0)</td>
<td>12 (5.8)</td>
<td>0.617</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Late outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>43 (18.6)</td>
<td>3 (13.0)</td>
<td>40 (19.2)</td>
<td>0.426</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>PPM</td>
<td>15 (6.5)</td>
<td>Pre-existing</td>
<td>15 (7.2)</td>
<td></td>
<td>15 (100)</td>
</tr>
<tr>
<td>MAZE with PPM</td>
<td>6 (2.6)</td>
<td>-</td>
<td>48 (23.1)</td>
<td></td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>1.000</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%). PPM, permanent pacemaker.
DISCUSSION

We identified a 30-day permanent pacemaker implantation rate of 10.0% after TVr which is in line with recent studies, collectively indicating that permanent pacemaker implantation rates following TVr are likely higher than previously thought. These findings are the result of a single-center analysis of TVr surgeries at Yale New Haven Hospital—an urban, mid-sized, academic center that included both isolated and concomitant TVr surgeries.

Gammie et al. report a 30-day permanent pacemaker implantation rate of 11.6% amongst patients with concomitant mitral valve repair (MVR) and tricuspid valve annuloplasty for secondary tricuspid regurgitation in an international multi-center prospective trial. Some previous reports of permanent pacemaker implantation with concomitant MVr and tricuspid valve annuloplasty were much lower, including Chikwe et al. who reported a permanent pacemaker implantation rate of 2.4% amongst 419 patients operated on by a single surgeon at a large, urban center and Brescia et al. who reported a rate of 4.1% among 171 patients at a single suburban academic center. Others, such as a study by Dzilic et al. report an early permanent pacemaker implantation rate of 8.5% at a single academic center in Germany, investigating three-dimensional tricuspid valve annuloplasty rings for functional tricuspid regurgitation with concomitant procedures. This study is useful in assessing the overall rate of permanent pacemaker implantation following tricuspid valve repair. While it is a single center, it is a representative American center that is urban and mid-sized with multiple surgeons included. This study also has
increased generalizability due to inclusion of both primary and secondary tricuspid valve
disease and isolated and concomitant procedures. These results are less generalizable to a
precise surgical populations as a heterogenous population were included to reflect the rate
of permanent pacemaker implantation after all tricuspid valve repairs at a single
institution.

Several studies have also looked at permanent pacemaker implantation following isolated
tricuspid valve surgery. Chen et al. recently performed a comprehensive analysis of
isolated tricuspid valve surgery including repairs and replacements. They identified a
permanent pacemaker implantation rate of 6% amongst repairs in a cohort that excluded
cases with infective endocarditis, mitral surgery, and aortic surgery, all of which could be
associated with increased rates of permanent pacemaker implantation and were included
in our cohort. Another report from Weiss et al., also focused on isolated tricuspid valve
surgery, demonstrated a permanent pacemaker implantation rate of 9.3%, although this
rate includes both tricuspid repairs and replacements.

There is significant variation in the reported rates of permanent pacemaker implantation
following tricuspid valve surgery. Some variation is expected, such as lower rates
amongst more experienced surgeons and higher rates amongst those undergoing
replacement compared to repair. There will also be some variation among different
patient populations and those undergoing different concomitant procedures, such as aortic
valve surgery, that can place them at higher risk for damage to the conduction system of
the heart.
Local practices regarding threshold for permanent pacemaker implantation and even time spent in the hospital postoperatively can influence pacemaker implantation rates. A longer length of stay postoperatively, such as in Europe compared to the United States, allows for greater opportunity to identify, and intervene, if considering a pacemaker. Part of the discrepancies could be related to how data is collected, particularly follow up data. Not all permanent pacemakers were implanted within the index operation, even if they were within 30-days, which, depending on the dataset used, might mean that fewer events are captured. Capturing events is even more difficult with patients receiving care within multiple different healthcare systems. There is also a potential financial incentive tied to pacemaker implantation that can play a role in differing rates of implantation.

Both patient risk factors and surgical risk factors can increase the risk of permanent pacemaker requirement in the setting of tricuspid valve repair. A downstream effect of chronic tricuspid regurgitation is right atrial enlargement which can increase the risk of atrial fibrillation in patients and contribute to overall sinus node disease. On top of the tricuspid valve disease contributing to conduction system disease, the tricuspid annulus is adjacent to several critical structures including the AV node and the bundle of His. When sutures are placed through an annuloplasty band or ring into the anulus, there is risk of damage to the nearby conduction structures. This creates a perfect storm of patients with preexisting conduction disorders undergoing a procedure with risk of further damage. While preexisting conduction disease is not necessarily an exclusion criterion for surgery,
it is something that is important to carefully evaluate prior to surgery and consider when assessing potential risks of surgery.

Understanding an accurate rate of permanent pacemaker implantation is important for understanding the risks associated with TVr, as is understanding the specific factors associated with increased risk of permanent pacemaker implantation. Better understanding and predicting of risks allow for better treatment selection for patients. Previous studies have suggested that redo surgery, concomitant mitral valve surgery, advanced age, and increased cardiopulmonary bypass time were associated with increased risk of permanent pacemaker implantation. In the univariate model, prior myocardial infarction and concomitant MAZE procedure were both approaching significance, but we did not find any statistically significant association between potential risk factors and permanent pacemaker implantation, although it is possible that this study was not sufficiently powered to detect significance for those variables.

One factor of particular interest is the MAZE procedure. The MAZE procedure was developed as a treatment for atrial fibrillation that creates a scar in the atrium that disrupts the electrical pattern in the atria by creating a MAZE of scar tissue. Cox et al. acknowledge that there can be damage to any number of parts of the electrical conduction system of the heart during the procedure, but suggest that the need for a permanent pacemaker following a MAZE procedure is that SA node dysfunction is further unmasked. Dzilic et al. found a highly significant association between MAZE and permanent pacemaker implantation requirement, all indicated for AV block. Others,
including the Ailawadi *et al.* follow up study from the CTSNet trial investigating permanent pacemaker implantation after concomitant tricuspid valve annuloplasty with concomitant MVr, did not find a significant association between MAZE procedure and early or late permanent pacemaker implantation. This study did not find a significant association between MAZE and permanent pacemaker implantation, although it was approaching significance.

The rates of later permanent pacemaker implantation after TVr in this study appear consistent with emerging reports. The two-year permanent pacemaker implantation incidence in this study was 14.3% which is similar to the 16% reported by Ailawadi *et al.* in their report of concomitant MVr and tricuspid valve annuloplasty. Leyva *et al.* describe the long-term risk of permanent pacemaker implantation following valve surgery, indicating that the risk is increased with double and triple valve surgery as well as age, male sex, emergency admission, diabetes mellitus, heart failure, and renal impairment.

The indications for permanent pacemaker implantation in this study, both early and late, appear consistent with the literature. About two-thirds of early permanent pacemaker implantations are for complete or high-degree AV block and one-third are for SA node dysfunction. While some report early permanent pacemaker implantation exclusively for AV node block, Ailawadi *et al.* and Mar *et al.* also indicate a similar proportion of AV and SA node indications in the perioperative period. The indications are flipped for late permanent pacemaker implantation, with the majority being for SA node dysfunction.
All of the patients in this study who required early permanent pacemaker implantation for SA node dysfunction had preoperative atrial fibrillation, which may indicate that surgery exacerbated an underlying pathology. Sinoatrial node dysfunction is less likely to be the direct result of surgery and rather an ongoing process that acutely worsened during the perioperative period. Further studies including those with electrocardiogram analysis both before and after surgery would be useful to better characterize the process for these patients.

Permanent pacemakers are not without risk to the patient. In this study period we did not observe an increased risk of death amongst patients that required permanent pacemaker implantation, but other studies have demonstrated a higher mortality rate amongst patients that are pacemaker dependent following cardiac surgery.\(^{47}\) Lead wires can actually cause damage to the tricuspid valve and any foreign materials in the heart increase risk of infection and endocarditis.\(^{48}\) Permanent pacing, particularly right ventricular pacing, can cause pacing induced cardiomyopathy as well.\(^{49}\) It is important that patients understand the risk of permanent pacemaker requirement following tricuspid valve surgery as they make an informed decision with their doctor.

In conclusion, permanent pacemaker implantation is not an uncommon occurrence following tricuspid valve repair surgery, with 10.0% of patients requiring permanent pacemaker implantation within 30 days of surgery primarily for high-grade and complete AV block, followed by SA node dysfunction. Permanent pacemaker requirement and implantation typically occur within 14 days of surgery.
CHALLENGES AND LIMITATIONS

This study had several challenges and limitations. This was a retrospective study, and not all relevant information was available for each patient. Patients may have had history of an arrhythmia that was not included in available health records or the STS database, or perhaps never identified at all prior to surgery, that contributed to their outcome after surgery.

Not all patients continued to receive care through our health system, so there was variability in the duration of follow up for patients. It is possible that patients have gone on to receive pacemakers or AICDs that were not captured in the data available. This also limited our ability to obtain the most accurate survival information. The inconsistent availability through the health information exchange may have introduced ascertainment bias. There is also a survival bias for those with late pacemaker implantation as only those that are still alive are eligible for the procedure.

This was a single center study which can reduce generalizability. Additionally, because this was a single-center study, there was a fixed number of patients that met inclusion criteria. We were unable to go further back in time due to limitations in the electronic health record. This reduced the power of the study and therefore the conclusions that we could draw from the results. Multivariate analyses were unable to be performed.

The population was heterogeneous, including patients with a variety of surgical indications, concomitant procedures, and comorbidities. When we initially began
discussing this project, it was focused on results from TVr with concomitant mitral valve surgery, but the potential implications reached beyond that specific population. We made the decision to include most tricuspid valve repairs, understanding that the heterogeneity allows us to make broader, but potentially less specific, conclusions. We also included a heterogeneous, although representative, sample of patients regarding preexisting conduction disorders, which allowed us to determine a more accurate rate of permanent pacemaker implantation but made the establishment of a direct causal pathway more difficult, particularly with SA node dysfunction.

Finally, surgeon expertise plays a role in the outcomes of tricuspid surgery. Tricuspid valve repair is not a common procedure and is most often performed at tertiary academic hospitals or other specialized centers. We did not include surgeon information in our analysis, but it is certainly an area that could be explored further.
DISSEMINATION

The authors were invited to share this work as a poster presentation at the American Association of Thoracic Surgeons 2023 Mitral Conclave meeting in New York, New York on May 4, 2023. The work was well received and part of a larger discussion around increasing frequency of tricuspid valve repair and possible implications. This work was also shared as a poster as part of the 2023 Yale Surgery Research Day, hosted by the Yale Department of Surgery, which allowed for discussion with classmates and colleagues. This work has been developed into a manuscript and is currently in submission.
Adult patients ≥18 years of age undergoing tricuspid valve surgery from 2014-2022 including those with concomitant CABG, mitral, aortic, and MAZE procedures (n=393)

- Exclude tricuspid valve replacements (n=84)
- Exclude tricuspid valvectomies (n=10)
- Exclude tricuspid valve repairs due to ventricular assist devices (n=10)
- Exclude tricuspid valve mass removals without valve repair (n=1)

Initial cohort of tricuspid valve repairs (n=288)

- Exclude patients with preexisting permanent pacemaker/AICD (n=53)
- Exclude cases with PPI during index operation (n=4)

Final cohort of tricuspid valve repairs (n=231)

**Figure 3.** Cohort inclusion criteria. AICD, automatic implantable cardioverter defibrillator; CABG, coronary artery bypass graft; PPI, permanent pacemaker implantation.
**Figure 4.** Timing of permanent pacemaker after tricuspid valve repair. AICD, automatic implantable cardioverter defibrillator; PPI, permanent pacemaker implantation.
Figure 5. Kaplan-Meier survival analysis based on early permanent pacemaker implantation after tricuspid valve repair surgery.


