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Conduction disorders and their clinical impact after sutureless/rapid deployment aortic bioprostheses

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Dedicatória

À minha família,

À minha Avó Luísa, por ser um brilhante exemplo de dedicação, trabalho, humildade e altruísmo. Por me ter transmitido sempre a sua Fé. Por todas as vezes que me deu a mão e disse comigo "eu sou capaz".

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Resumo

Introdução: A estenose aórtica é a principal patologia valvular cardíaca. O impulso para melhorar os resultados da cirurgia de substituição valvular aórtica (SVA), que permanece como *gold standard*, levou a um interesse crescente numa nova geração de próteses, as válvulas aórticas de *rapid deployment/sutureless*. Estas próteses levam a uma redução dos tempos de clampagem da aorta e *bypass* cardiopulmonar e de isquémia do miocárdio. São também benefícios da utilização destas próteses uma menor duração do procedimento, diminuição dos tempos de estadia no hospital, taxas de complicações reduzidas e maiores taxas de sobrevivência. No entanto, devido à sua estrutura e método de implantação, alguns centros reportaram um aumento dos distúrbios de condução e de implantação de *pacemaker* permanente, associados à utilização de próteses de *rapid deployment*.

Objetivos: O objetivo deste estudo foi investigar a incidência de distúrbios de condução elétrica após cirurgia de substituição valvular aórtica, com recurso a válvulas de *rapid deployment*. Investigou-se também o impacto sobre os resultados pós-operatórios imediatos e a incidência de outras implicações pós-operatórias, tais como a implantação de *pacemaker* permanente.

Métodos: Todos os doentes que foram submetidos a cirurgia de substituição valvular aórtica isolada entre as datas de 14/05/2014 e 17/12/2019, em um único hospital, foram incluídos. Doentes que requereram um procedimento adicional, com implantação de *pacemaker* prévia, casos de re-operação e doentes com dados de ECG, pré ou pós-operatórios, em falta, foram excluídos deste estudo. A população foi dividida em dois grupos, grupo "PPM" (com implantação de *pacemaker* permanente) e grupo "No PPM" (sem implantação de *pacemaker* permanente), que foram comparados. O objetivo primário deste estudo foi a análise de implantação de *pacemaker* permanente e o seu impacto no pós-operatório. Objetivos secundários incluíram tempos cirúrgicos, distúrbios de condução e de ritmo pós-operatórios, complicações clínicas pós-operatórias e identificação de fatores de risco para implantação de *pacemaker* permanente.

Resultados: Foram estudados 201 doentes. Globalmente, 26 *pacemakers* permanentes foram implantados (12.9%).

Análises uni e multivariável encontraram um fator de risco independente associado a implantação de *pacemaker* permanente: bloqueio completo de ramo direito pré-operatório (OR 11.7, p=0,001 e OR 7.28, p=0.020, análises uni e multivariável respetivamente). O grupo "PPM" revelou mais bloqueios completos de ramo esquerdo pré-operatórios (21.1% vs 11.6%, p<0.001) e bloqueios completos de ramo direito (26.3% vs 3.6%, p<0.001). Este grupo apresentou também estadias mais longas na UCI (4.7 ± 2.9 vs 2.8 ± 2.7, p=0.003) e no hospital (10.0 ± 6.2 vs 6.1 ± 3.4, p=0.005). A nível pós-operatório, o grupo "PPM" apresentou mais AVC (7.7% vs 0.0%, p=0.016) e mais necessidade de suporte aminérgico durante mais de 24 horas (60.0% vs 36.1%, p=0.028). Os restantes resultados não apresentaram diferenças estatisticamente significativas entre os dois grupos.

Conclusões: Este estudo encontrou uma percentagem de implantação de *pacemaker* permanente, após cirurgia de substituição valvular aórtica com próteses de *rapid deployment*, de 12.9%. Doentes que requereram implantação de pacemaker permanente demonstraram estadias na unidade de cuidados intensivos (UCI) e no hospital, taxas de acidente vascular cerebral (AVC) pós-operatório e necessidade de suporte aminérgico por mais de 24 horas, significativamente maiores. Bloqueio completo de ramo direito pré-operatório foi identificado como o único fator de risco independente para implantação intra-hospitalar de *pacemaker* permanente.

Palavras-chave

Cirurgia cardíaca; substituição valvular aórtica; próteses de *rapid deployment*; implantação de *pacemaker*; bloqueio atrioventricular completo.

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Abstract

Background: Aortic stenosis remains the number one heart valve pathology and its prevalence keeps increasing. The drive to improve the outcomes of SAVR, which remains as the gold standard treatment, brought to focus a new generation of bioprostheses, rapid deployment aortic valves (RDAV) and sutureless valves. These prostheses reduce aortic cross-clamping and CPB duration as well as myocardial ischemia. Shortening of procedure duration, shorter ICU and hospital stays, lower complication rates and better survival rates, are among some of the other expected benefits of using these bioprostheses. However, due to its structure and implementation method, some centers have reported a higher rate of conduction abnormalities and PPM implantation with rapid deployment bioprostheses.

Objectives: The aim of this study was to investigate the incidence of conduction abnormalities after aortic valve replacement with rapid deployment/sutureless bioprostheses as well as its impact on immediate postoperative outcomes and other postoperative implications, such as permanent pacemaker (PPM) implantation.

Methods: All patients undergoing aortic valve replacement between 14/05/2014 and 17/12/2019, in one center, were included. Patients requiring an additional procedure, with previous pacemaker implantation, reoperation cases and patients with missing pre or postoperative ECG data, were excluded from this study. Our cohort was divided into 2 groups, "PPM" group and "No PPM" group, that were compared. The primary end point was permanent pacemaker implantation and its postoperative outcomes. Secondary end points included operatory times, conduction and rhythmic postoperative disorders, clinical postoperative complications and identification of risk factors for in-hospital PPM implantation.

Results: We studied 201 patients, all of which underwent isolated aortic valve replacement with a rapid deployment bioprosthesis. Overall, 26 PPM were implanted (12.9%). The uni and multivariate analysis found one independent risk factor associated with in-hospital PPM implantation: preoperative right bundle branch block (RBBB) (OR 11.7, p=0,001 and OR 7.28, p=0.020 for uni and multivariable analysis respectively). "PPM" group had more preoperative left bundle branch block (21.1% vs 11.6%, p<0.001) as well as right bundle branch block (26.3% vs 3.6%, p<0.001).

"PPM" group also presented with longer ICU (4.7 ± 2.9 vs 2.8 ± 2.7, p=0.003) and hospital (10.0 ± 6.2 vs 6.1 ± 3.4, p=0.005) stays. Postoperatively, the "PPM" group had higher rates of stroke (7.7% vs 0.0%, p=0.016) and requirement of aminergic support for longer than 24 hours (60.0% vs 36.1%, p=0.028). There were no statistically significant differences between the two groups among the other outcomes studied.

Conclusions: This study found a 12.9% rate of permanent pacemaker implantation after AVR with rapid deployment bioprostheses. Patients that required PPM implantation had significantly higher hospital and ICU stays, postoperative stroke rates and requirement of aminergic support for longer than 24 hours. Preoperative RBBB was identified as the single independent risk factor for in-hospital PPM implantation.

Keywords

Cardiac surgery; aortic valve replacement; rapid deployment bioprostheses; pacemaker implantation; complete atrioventricular block.

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Abbreviations

SAVR	Surgical Aortic Valve Replacement
RDAV	Rapid Deployment Aortic Valve
PPM	Permanent Pacemaker
RBBB	Right Bundle Branch Block
LBBB	Left Bundle Branch Block
ICU	Intensive Care Unit
AVR	Aortic Valve Replacement
TAVI	Transcatheter Aortic Valve Implantation
CPB	Cardiopulmonary Bypass
EuroScoreII	European System for Cardiac Operative Risk Evaluation
AV	Atrioventricular
LV	Left Ventricle
OR	Odds Ratio
CI	Confidence Interval
CAVB	Complete Atrioventricular Block
PVL	Paravalvular Leakage
CO	Cardiac Output
AVB	Atrioventricular Block

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Chapter 1

Introduction

Aortic stenosis remains the number one heart valve pathology and its increasingly prevalence is mainly explained by the ageing population. Surgical replacement or transcatheter percutaneous implantation are presently the available treatments based on patients surgical risk. (1)

Early therapy is strongly recommended in all symptomatic patients with severe aortic stenosis due to its poor spontaneous prognosis. (2) More recently it's even starting to be recommended for asymptomatic patients with signs of cardiac damage. (3) Exceptions are patients with severe comorbidities with an expected survival of less than one year and patients in whom underlying comorbidities or their general condition at an advanced age make it unlikely that the intervention will improve quality of life or survival. (4)

Regarding the choice of the intervention mode, surgical aortic valve replacement (SAVR) remains as the standard treatment. Nevertheless, acute kidney injury, severe bleeding and new-onset atrial fibrillation are still significantly more frequent with surgery. (4)

As an alternative to SAVR, transcatheter aortic valve implantation (TAVI) is progressively becoming more sought-after. First evidence of comparable results of TAVI and SAVR was found in intermediate and high-risk patients and more recently, two prospective industry-sponsored trials (EVOLUT and PARTNER3) demonstrated, at least, non-inferiority of the TAVI approach in low risk patients.

These findings stimulated the drive to continue improving the outcomes of SAVR. Conventional AVR frequently uses tissue valves which require extensive suturing leading to increased cardiopulmonary bypass (CPB) and cross-clamp times. Efforts have recently been focused in a new generation of bioprostheses, rapid deployment aortic valves (RDAV) and sutureless valves.

Sutureless and RDAV are pericardial bioprostheses that are anchored within the aortic annulus with a maximum of three sutures.

Two types of this kind of prostheses are presently available at the market, namely Perceval S (Sorin, Salugia, Italy) and Intuity Elite (Edwards Lifesciences, Irvine, USA). (5)

The Perceval valve is comprised of both a biological portion of bovine pericardium as well as a super-elastic alloy metal cage to which the former is attached. Due to its elasticity the stent is able to adapt to the aorta and its movements, therefore relieving stress on the leaflets. Until the valve is in the right position it remains collapsed by an atraumatic compression device, preventing damage to the leaflets. Only then Perceval self-expands to its original diameter. (5)

The Intuity valve system is not considered to be a pure sutureless bioprosthesis but rather a RDAV. It is a bovine pericardial prosthesis comprised of a stent-based deployment system, reducing to three the number of sutures used to attach the prosthesis to its final position. (6)

Sutureless and rapid deployment prostheses reduce aortic cross-clamping and CPB duration as well as myocardial ischemia, by reducing the need for sutures after annular decalcification. (7, 8) Shortening of procedure length is also thought to be an advantage as it may help reducing postoperative morbidity and mortality as well as improving cost-effectiveness, particularly in patients undergoing concomitant procedures. (5) Shorter hospital stays, lower complication rates and better survival rates are also verified when compared with conventional AVR. (8)

Conduction disorders, sometimes requiring permanent pacemaker (PPM) implantation, are well known complications of AVR. The rate of PPM implantation with conventional aortic valves is ≈ 5%. Due to its structure and implementation method, some centers reported a higher rate of conduction abnormalities and PPM implantation (between 8,5% and 17%) with rapid deployment bioprostheses. (9)

The aim of this study is to investigate the incidence of conduction abnormalities after isolated AVR with RDAV as well as its impact on immediate postoperative outcomes and other postoperative implications, such as PPM implantation.

Chapter 2

Materials and Methods

2.1. Patients

Data of all adult patients who underwent isolated aortic valve replacement between 14/05/2014 and 17/12/2019 in the cardiothoracic surgery department of one teaching hospital (Hospital de Santa Maria, Lisbon, Portugal) were retrospectively collected and reviewed. Patients requiring an additional procedure as well as patients with previous pacemaker implantation, were excluded. Reoperation cases and patients with missing pre or postoperative ECG data were also left out from this study.

From a total of 450 aortic valve implantations, we ended up with 201 patients after the application of the exclusion criteria. Those patients were then divided into two groups: "No PPM" group, composed of 175 patients and "PPM" group, with 26 patients (Figure 1). Patients included in this study were submitted to either a conventional surgical technique or a minimally invasive approach.

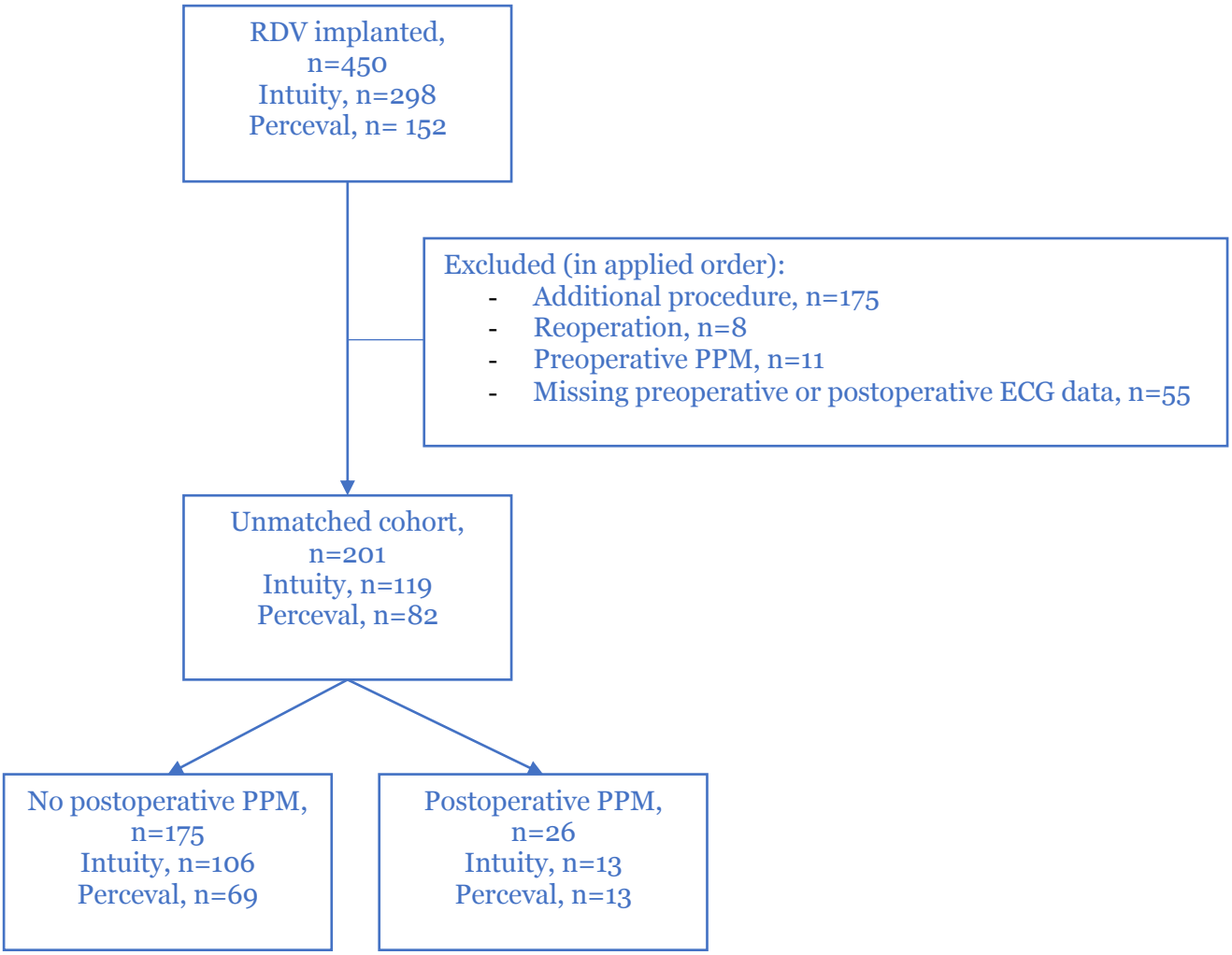
Indications for AVR were in concordance with the European guidelines at the time of the interventions. The choice between using a pure sutureless bioprosthesis (Perceval valve) or a RDAV (Intuity valve system) was left to the surgeon's judgement.

The analysis of the database required for this study was approved by the hospital's ethics committee (identification number: 510/18).

Preoperative and postoperative clinical, echocardiogram and echocardiographic data were collected from the patients' medical records, namely preoperative comorbidities, EuroScore II, presence of atrial fibrillation, pacemaker, LV function and previous cardiac surgery. Operatory data (aortic clamping time, cardiopulmonary bypass time, type and size of the bioprostheses), in-hospital stay and postoperative complications were also collected. Data from preoperative and postoperative electrocardiogram were obtained.

The primary end point was the rate of postoperative PPM implantation. Secondary end points included: operatory times (aortic clamping and cardiopulmonary bypass times); conduction and rhythmic postoperative disorders [defined as first degree AV block, left bundle branch block (LBBB), right bundle branch block (RBBB), atrial fibrillation/flutter, complete atrioventricular block and slow atrial fibrillation]; clinical postoperative complications, including abnormal bleeding, surgical exploration for bleeding, new-onset atrial fibrillation, significant renal dysfunction, renal replacement support, stroke, aminergic support > 24h, intra-aortic balloon pump and infection; and identification of risk factors for in-hospital PPM.

Figure 1: Study flow chart.



RDV – rapid deployment valve, PPM - permanent pacemaker.

2.2. Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics v26. Continuous variables were treated as mean and standard deviation and compared with Student's t-test. Categorical variables were summarized as the number and/or percentage of subjects in each category and compared with Chi square/Fisher's exact tests, as appropriate. Factors associated with new-onset conduction disorders and PPM implantation were assessed using a multivariable logistic regression model. Variables screened as potential confounders were the preoperative baseline characteristics and operative details and the ones considered to be of clinical significance were conducted through univariable significance testing. All variables with a p-value of less than 0.10 upon univariable analysis were pondered as having a potential confounding effect and were included in the multivariable model. Using this strategy, the following variables were included in the model: preoperative atrial fibrillation, preoperative first-degree atrioventricular block, preoperative left bundle branch block, preoperative right bundle branch block, large prosthesis (Intuity 25 and 27, Perceval L and XL), and type of prothesis (Intuity, Perceval). Variables with a p-value of less than 0.05 were retained in the final multivariable model.

Chapter 3

Results

3.1. Preoperative results

Between May 2014 and December 2019, 201 patients were included. Amongst these patients 26 (12.9%) underwent PPM implantation. Preoperative baseline characteristics of the cohort are shown in Table 1 and these included demographics, Euroscore II, risk factors and major comorbidities. The “PPM” and “No PPM” groups were compared.

The mean overall age was 75.8 ± 6.04 and 50.2% of the entire cohort were females. EuroScore II predicted a risk of 2.27 ± 1.56.

The most prevalent preoperative comorbidities within the 201 patients were arterial hypertension (93.5%), impaired renal function (80.0%), dyslipidemia (76.1%) and overweight/obesity (75.1%).

Coronary disease was present in 28.9% of the cohort, 18.9% presented with atrial fibrillation of any form and 6.5% with an history of stroke or transient ischemic attack. The vast majority (82,6%) of the patients had preserved left ventricular function.

The two groups (PPM, No PPM) were very similar in terms of baseline characteristics. The “PPM” group had significantly higher preoperative rates of diabetes mellitus (57.7% vs 30.9%, p=0.013) as well as dyslipidemia (92.3% vs 73.7%, p=0.047). The remaining characteristics presented with no significant differences.

Table 1 - Preoperative characteristics.

	All (n=201)	No PPM (n=175)	PPM (n=26)	p
Sex (female)	50.2%	51.4%	42.3%	0.409
Age (years)	75.8±6.04	75.9±6.18	75.7±5.17	0.900
EuroScore II (%)	2.27±1.56	2.29±1.61	2.12±1.10	0.492
Arterial hypertension	93.5%	92.6%	100.0%	0.225
Dyslipidemia	**76.1%**	**73.7%**	**92.3%**	**0.047**
Impaired renal function[1]	80.0%	80.1%	79.2%	1.000
Overweigh/obesity[2]	75.1%	74.9%	76.9%	1.000
Coronary disease	28.9%	26.3%	46.2%	0.061
Diabetes Mellitus	**34.3%**	**30.9%**	**57.7%**	**0.013**
Insulin treated	3.0%	2.9%	3.8%	0.569
Atrial fibrillation[3]	18.9%	19.4%	15.4%	0.791
Respiratory disease	21.9%	22.3%	19.2%	1.000
Smoking history[4]	19.9%	19.4%	23.1%	0.609
Peripheral artery disease	5.0%	4.6%	7.7%	0.621
Pacemaker	0.0%	0.0%	0.0%	1.000
Previous stroke or transient ischemic attack	6.5%	6.3%	7.7%	0.678
Preserved LV function	82.6%	82.9%	80.8%	0.491

PPM – permanent pacemaker, LV – Left ventricle.
Categorical variables are presented as percentage of subjects in each category. Continuous variables were treated as mean and standard deviation.
[1] Impaired renal function was defined as glomerular filtration rate <80%.
[2] Overweigh/obesity was defined as body mass index >25.
[3] Any form: paroxysmal, persistent, permanent.
[4] Former or active.

3.2. Intraoperative and postoperative results

Intraoperative and postoperative characteristics of “PPM” and no “No PPM” groups are shown in Table 2.

Regarding the operatory data (aorta clamping time, cardiopulmonary bypass and type of valve) there were no significant differences between the two groups. Mean aortic clamping time in minutes was 27.3 ± 8.4 and mean cardiopulmonary bypass time (minutes) was 36.5 ± 11.4. Concerning the type of bioprostheses used, 59.2% of all patients received an Intuity valve while 40.8% were implanted with a Perceval bioprostheses. As for the size of the bioprostheses, number 23 (n=40) was the most used one amongst the Intuity bioprostheses, followed by the numbers 21 (n=32) and 25 (n=31). Amidst the Perceval valves, size M (n=30) was the most implanted one followed by size L (n=25).

Concerning the in-hospital stay data analysis, a significant difference was found between the two groups. Both ICU stay (4.7 ± 2.9 vs 2.8 ± 2.7, p=0.003) and hospital stay (10.0 ± 6.2 vs 6.1 ± 3.4, p=0.005), in days, were significantly higher in the “PPM” group.

With respect to the postoperative complications, the most prevalent ones over the entire cohort were aminergic support for over 24 hours (39.4%), significant renal dysfunction (25.9%), new onset atrial fibrillation (21.9%) and abnormal bleeding (16.4%). Less widespread postoperative complications were surgical exploration for bleeding (4.5%), infection (4.5%), renal replacement support (2.0%), stroke (1.0%) and intra-aortic balloon pump (1.0%). In-hospital mortality was the overall less prevalent postoperative complication (0.5%).

The two groups showed little differences in regard to most complications. However, the “PPM” group showed significantly higher rates of stroke (7.7% vs 0.0%, p=0.016) and aminergic support for longer than 24 hours (60.0% vs 36.1%, p=0.028).

Table 2 - Intraoperative and postoperative characteristics.

	All (n=201)	No PPM (n=175)	PPM (n=26)	P
Operatory data				
Aorta Clamping (minutes)	27.3±8.4	27.1±8.7	28.3±6.1	0.400
Cardiopulmonary bypass (minutes)	36.5±11.4	36.5±12.0	37.0±7.0	0.725
Intuity valve	59.2%	60.6%	50.0%	0.393
n°19 (*n*)	14	13	1	
n°21 (*n*)	32	30	2	
n°23 (*n*)	40	35	5	
n°25 (*n*)	31	27	4	
n°27 (*n*)	2	1	1	
Perceval valve	40.8%	39.4%	50.0%	0.393
S (*n*)	11	10	1	
M (*n*)	30	26	4	
L (*n*)	25	21	4	
XL (*n*)	16	12	4	
In-hospital stay				
ICU stay (days)	**3.0±2.8**	**2.8±2.7**	**4.7±2.9**	**0.003**
Hospital stay (days)	**6.6±4.1**	**6.1±3.4**	**10.0±6.2**	**0.005**
Post-operative complications				
Abnormal bleeding[2]	16.4%	15.4%	23.1%	0.392
Surgical exploration for bleeding	4.5%	4.0%	7.7%	0.328
Atrial fibrillation *de novo*	21.9%	23.4%	11.5%	0.211
Significant renal dysfunction[3]	25.9%	25.7%	26.9%	1.000
Renal replacement support[4]	2.0%	1.7%	3.8%	0.428
Stroke	**1.0%**	**0.0%**	**7.7%**	**0.016**
Aminergic support[5] >24h	**39.4%**	**36.1%**	**60.0%**	**0.028**
Intra-aortic balloon pump	1.0%	0.6%	3.8%	0.243
Infection[6]	4.5%	4.0%	7.7%	0.328
In-hospital mortality	0.5%	0.6%	0.0%	1.000

ICU - Intensive care unit, PPM – permanent pacemaker.

Categorical variables are presented as percentage of subjects in each category and compared with t-student tests. Continuous variables were treated as mean and standard deviation and compared with Fisher's exact tests.

[1] Transfusion of at least 1 unit.

[2] Abnormal bleeding was defined as > 2ml/kg/h in the first 2-3 hours, > 1ml/kg/h in the next 3 hours and/or > 0.5ml/kg/h in 12 hours.

[3] Significant renal dysfunction was defined as KDIGO stages 2 and 3.

[4] Renal replacement support was performed through Continuous Veno-Venous Hemodiafiltration.

[5] Aminergic support was performed with at least one of the following: epinephrine, norepinephrine, dobutamine.

[6] Respiratory, urinary and/or blood infection.

3.3. Rhythm

Preoperative and postoperative data regarding cardiac rhythm can be found in Table 3.

Patients with preoperative complete atrioventricular block were excluded from this study. Amongst the preoperative rhythm data, left bundle branch block (21.1% vs 11.6%, p<0.001) and right bundle branch block (26.3% vs 3.6%, p<0.001) were significantly higher in the "PPM" group.

Evaluation of postoperative rhythm revealed that the majority of PPM implantations followed a complete atrioventricular block (92.3%) with only two patients (7.7%) following slow atrial fibrillation. Amidst the "No PPM" group, the majority of the conduction abnormalities were left bundle branch block (54.0%), followed by first degree atrioventricular block (26.8%), atrial fibrillation/flutter (9.7%) and right bundle branch block (6.7%).

Table 3 – Rhythm.

	All (n=201)	No PPM (n=175)	PPM (n=26)	P
Preoperative rhythm				
Sinus	89.6%	89.1%	92.3%	1.000
+ First degree atrioventricular block	14.9%	13.6%	25.0%	0.261
+ Left bundle branch block	**12.7%**	**11.6%**	**21.1%**	**<0.001**
+ Right bundle branch block	**6.4%**	**3.6%**	**26.3%**	**<0.001**
Atrial fibrillation/Flutter	10.4%	10.9%	7.7%	1.000
Postoperative rhythm				
Sinus	78.6%	90.3%		
+ First degree atrioventricular block	22.8%	26.8%		
+ Left bundle branch block	46.6%	54.0%		
+ Right bundle branch block	5.7%	6.7%		
Atrial fibrillation/Flutter	8.5%	9.7%		
Complete atrioventricular block (-> PPM)	11.4%		92.3%	
Slow Atrial fibrillation (-> PPM)	1.0%		7.7%	

PPM – permanent pacemaker.

3.4. AVR and PPM implantation per year and bioprostheses

Distribution of cases and PPM implantation rates per year and valve prostheses is represented in Table 4.

Out of a total of 201 patients, 119 (59.2%) received an Intuity valve system and the remaining patients had a Perceval bioprostheses being implanted. The majority of the AVR surgeries happened during 2016-2017 (n=106), followed by 78 during 2018-2019 and 17 during 2014-2015.

Regarding PPM implantation, 12.9% of the overall cohort received a PPM, which represented 15.9% of patients with a Perceval valve and 10.9% of patients with an Intuity bioprostheses.

Total PPM implantation rates show a continuous decrease through the years: 17.6% in 2014-2015, 17.0% in 2016-2017 and 6.4% in 2018-2019. The same can be inferred within the Perceval group: 50.0% in 2014-2015, 22.0% in 2016-2017 and 7.7% in 2018-2019. In the Intuity group, despite of a small increase in PPM implantation rates from 2014-2015 (13.3%) to 2016-2017 (13.8%), there was a decrease in the following years – 2018-2019 (5.1%).

Table 4 – Distribution of cases per year and valve prostheses.

		Intuity	Perceval	Total
2014-2015	Total	15	2	17
	PPM	13,3%	50,0%	17,6%
2016-2017	Total	65	41	106
	PPM	13,8%	22,0%	17,0%
2018-2019	Total	39	39	78
	PPM	5,1%	7,7%	6,4%
Total	Total	119	82	201
	PPM	10,9%	15,9%	12,9%

PPM – permanent pacemaker.

3.5. Univariate and multivariate analysis of risk factors for in-hospital PPM

The preoperative and operatory risk factors associated with PPM implantation after AVR are presented in Table 5.

In this univariate analysis, only preoperative RBBB (OR 11.7; 95% CI 2.89-47.3; p=0.001) was associated with PPM implantation.

A multivariate analysis was run by stepwise logistic regression to determine which independent risk factors were associated with PPM implantation. Preoperative RBBB was revealed as the single independent risk factor for in-hospital PPM implantation (OR 11.7, p=0,001 and OR 7.28, p=0.020 for uni and multivariable analysis respectively).

The type and size of the bioprosthesis were not associated with PPM implantation.

Table 5 - Risk Factors for In-hospital Permanent Pacemaker Implantation.

	Univariate Analysis		Multivariate Analysis	
Risk Factor	OR (95% CI)	p	OR (95% CI)	p
Preoperative atrial fibrillation	1.46 (0.32-6.68)	0.624		
Preoperative first-degree atrioventricular block	2.11 (0.61-7.27)	0.236		
Preoperative LBBB	2.92 (0.82-10.4)	0.098	1,85 (0,43-7,90)	0,405
Preoperative RBBB	**11.7 (2.89-47.3)**	**0.001**	**7,28 (1,37-38,64)**	**0,020**
Large prosthesis*	1.87 (0.82-4.3)	0.139		
Type of prothesis	1.54 (0.672-3.51)	0.309		

CI – confidence interval, LBBB - left bundle branch block, OR – odds ratio, RBBB - right bundle branch block.
*Intuity 25 and 27, Perceval L and XL.

Chapter 4

Discussion

Rapid deployment aortic valves (RDAV) represent an alternative to conventional bioprostheses in aortic valve replacement (AVR). These prostheses present with excellent haemodynamic results (10), reducing aortic cross-clamping and cardiopulmonary bypass times as well as myocardial ischemia. This is thought to cause reduced postoperative morbidity and mortality as well as improved cost-effectiveness. This explains why its use in AVR has spread. Nevertheless, these new bioprostheses have been associated with higher rates of postoperative complete atrioventricular block (CAVB), ultimately requiring PPM implantation. PPM implantation rates following AVR with RDAV have been described in the scientific literature with great variability, with values falling between 8% and 23% (10). This reflects far higher percentages than those obtained in AVR with conventional prostheses (≈ 5%). (11)

The first goal of our study was to investigate the incidence of PPM implantation after isolated AVR with RDAV. In a cohort of 201 patients, 26 required postoperative PPM implantation, translating into a 12.9% rate of permanent pacemaker implantation.

Secondly, we aimed to study the postoperative characteristics of our population in order to reach conclusions about the impact of new PPM implantation after AVR.

We began by verifying significantly higher hospital and ICU stays which has been explained by the late diagnosis of rhythm disturbances and the requirement for prolonged monitoring (12). This has been reported to translate into increased resource use (12) as well as a delay in patients' recovery after AVR (13).

Significantly higher rates of postoperative stroke were also verified in the "PPM" group. Even though the reason behind this finding remains unclear, there are some particularities of RDAV that may explain it. First of all, these bioprostheses have unique stent frame and leaflet designs. Experience regarding their potential influence on thrombus formation, and consequent stroke risk, is still limited.

A previous study has commented on the high rate of subclinical leaflet thrombosis following sutureless valve implantation. (14) On the other hand, specific recommendations regarding anticoagulation regimen after AVR with RDAV, still don't exist.

Moreover, the extent of annular calcification is thought to play a big role in stroke pathophysiology as well as in conduction disorders. Patients whose aortic annulus have a higher content of calcium are at higher risk for embolization during annular decalcification and heart block from annular or subannular extension.

Adding to this, it was initially recommended to not entirely decalcify the aortic annulus before RDAV implantation to prevent inadequate decalcification, which could lead to an uneven surface and in turn, to paravalvular leakage (PVL). It is thought that remaining (or partly mobilized) calcium deposits could break off after valve implantation and lead to stroke (15). Opposite to initial recommendations, more recent studies (10) have reported modifying their technique, advocating for a more thorough decalcification in order to avoid the impaction of calcium against the conduction system, and thus decreasing AVB incidence. However, we can rule out this explanation that a change in the decalcification technique could have been responsible for a modification in the postoperative stroke and pacemaker rates at our center, as the decalcification technique (complete annular decalcification) has remained the same during the entire time period being studied.

Atrioventricular conduction disorders leading to PPM implantation and postoperative stroke, share some underlying mechanisms. As described above, calcification may also be the mechanism behind the development of conduction disorders as the high pressure at the level of the membranous septum may damage the bundle of His and the atrioventricular conduction system (16). It can then be speculated that the higher incidence of postoperative stroke in the "PPM" group is somewhat related to the extension and manipulation of calcium.

Lastly, requirement of aminergic support for longer than 24 hours was also found to be significantly higher in the "PPM" group. Temporary epicardial pacemakers, the most frequently implanted type of PM following cardiac surgery, pace the ventricles in isolation. The physiologic electrical synchronization of atria and ventricles are altered whenever a pacing device is implanted, often leading to improper or mistimed atrial and ventricular contraction (17).

Since optimal atrioventricular (AV) synchrony can increase the cardiac output (CO) between 25 and 30% (14), PM implantation can ultimately cause a reduction in CO, leading to the requirement of longer aminergic support by the "PPM" group.

Additionally, our study also sought to identify the risk factors that could be directly related to PPM implantation after AVR with rapid deployment bioprostheses. Several other studies have previously tried to identify these risk factors (11).

We began by analyzing the preoperative rhythm of our cohort (Table 3), observing that both left bundle branch block and right bundle branch block were significantly more frequent in the "PPM" group. A multivariate analysis was further performed, identifying preoperative RBBB as the single independent risk factor for in-hospital PMM implantation. RBBB had previously been described as a risk factor for postoperative conduction disturbances requiring PPM (18).

Furthermore, postoperative rhythms of our patients were also studied (Table 3). LBBB was identified as the most frequent postoperative conduction disorder presenting itself in 46.6% of all the patients who underwent AVR with RDAV. It has been previously described that the anatomical relationship of the bioprosthesis with the membranous septum, where the shared portion of the left bundle of His is found, might exert a direct influence (18). On one hand, this anatomical predisposition of the left bundle of His to injury would explain why preoperative LBBB is not an independent risk factor for PPM implantation – electrical stimulation would be transmitted in a similar way to what happened before the surgery. However, patients with no conduction abnormalities prior to the surgery would have a greater frequency of postoperative LBBB – as our study seems to show. On the other hand, this would also explain why patients with preoperative RBBB are at increased risk for PPM implantation; damage to the only previously healthy bundle branch (left bundle branch) would lead to a complete atrioventricular block and consequent PPM implantation.

Not the type of prosthesis nor the use of large prostheses, classified as Intuity 25 and 27 and Perceval L and XL, were identified as independent risk factors for PPM implantation.

Other studies (18, 19) concluded that is the oversizing rather than the isolated large valve size which is responsible for greater numbers of paravalvular leaks and an increase of valvular gradients (due to valve underexpansion) ultimately leading to valve dysfunction.

An oversized bioprosthesis tends to recoil, leading to loss of contact between the prosthesis and the annulus which could be responsible for altered kinetics of the leaflets, incomplete valve opening, increased gradients, paravalvular leakage and possibly important aortic regurgitation.

A high incidence of postoperative AVB has also been reported (10) when patients were implanted with a large sized (L or XL; 25 or 27) prosthesis.

To address this problem, manufacturers recommended choosing the smaller valve size when hesitating between two sizes. In the specific case of Perceval S, a group of researchers went further and recommended modifying the sizing method and implanting the valve size given by the sizer when the white obturator (larger) passes through the annulus with friction (19).

Regarding our cohort, looking into the distribution of cases per year and valve prosthesis (Table 4), we can conclude that there is a continuous decrease in PPM implantation rates through the years, especially between the years of 2017, with a 17% rate of PPM implantation, and 2018, with a PPM implantation rate of 6.4%.

One of the reasons that justifies this considerable decrease is the change in the PPM implantation methods in our center, starting in 2018, when the sizing method recommendations were altered in order to prevent oversizing.

We can further speculate that this downward tendency in PPM implantation over de years can be related to the effect of the learning curve as well as the surgeon experience.

Chapter 5

Conclusions

Rapid deployment aortic bioprostheses implantation, with both Intuity and Perceval valves, was associated with a 12.9% rate of PPM implantation. This stands within the PPM implantation rate intervals which have been previously reported. The choice of this type of bioprosthesis reduces aortic cross-clamping and cardiopulmonary bypass times, myocardial ischemia and yields excellent haemodynamic results. However, increased postoperative complications like PPM implantation, need to be taken in consideration. In order to maximize the benefit/risk ratio, the final decision whether or not to use RDAV should be made on a case-by-case basis, considering the existence of both preoperative conduction disorders, especially right bundle branch block, and extension of annular calcification.

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