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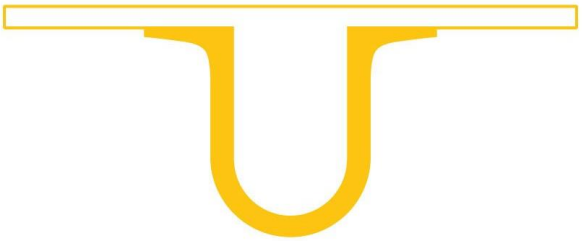

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

BEATRIZ FALCÃO DE ALMEIDA CARDOSO

A Systematic Review on the Use of Pacemakers in Pediatric Patients

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE CARDIOLOGIA PEDIÁTRICA

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I. ABSTRACT

There is a relative diminished experience in cardiac pacemaker (PM) implantation in pediatric patients regarding type and mode of implantation, indications and complications thus, there is very little consensus even among experts in the field. Since there is a lack of clearly defined guidelines created for children and focusing on all the particularities related to them, the aim of this systematic review is to appraise the available literature on the indications for permanent cardiac pacing, the most adequate pacing type (epicardial vs. endocardial), the best suited pacing mode (single-chamber vs. dual-chamber) and the most common complications associated with these types of cardiac implantable devices.

We searched MEDLINE®, EMBASE®, Web of Science, The Cochrane Library and ClinicalTrials.gov for original articles written in English or Portuguese, published from 01/01/2000 to 12/31/2018 by using the appropriate MeSH controlled vocabulary – pacing, pacemaker, child, pediatric - in combination with database-specific filters when available.

Permanent cardiac pacing in pediatric patients appears to be an overall safe procedure with good short-, medium- and long-term results. However, there is a high rate of complications, mainly lead-related, especially in younger and smaller children. And so, it is suggested that PM implantation should be reserved for patients who weight more than 3 Kg and who are older than 5 days of age. The initial choice between transvenous and epicardial pacing should be made according to patient characteristics, need for cardiac surgery and available experience in the unit treating these patients with preferential preservation of vascular access in younger patients so that later on, a switch can be made from epicardial to endocardial given that endocardial pacing has better long-term results. Single-chamber pacing should be used as a bridge to a later upgrade to physiological pacing since dual-chamber pacing is the best alternative at long-term follow-up.

KEYWORDS

PEDIATRICS; CARDIOLOGY; ARTIFICIAL CARDIAC PACEMAKER; ATRIOVENTRICULAR BLOCK; SINUS NODE DYSFUNCTION

II. LIST OF ABBREVIATIONS

AV: Atrioventricular

AVB: Atrioventricular Block

CHD: Congenital Heart Disease

CCAVB: Complete Congenital Atrioventricular Block

LV: Left Ventricle

PM: Pacemaker

SE: Steroid-Eluting

SND: Sinus Node Dysfunction

III. INTRODUCTION

Artificial cardiac pacing in children accounts for less than 1% of all pacemaker implantations(1). Not only does this translate a relative diminished experience in its implantation, but also in its indications and complications and as such there is very little consensus among even experts in the field.

According to the 2013 ESC Guidelines(2), the most recent guidelines on cardiac pacing, the major indications (Class I) for pacing in pediatric patients are: 1) high degree and complete atrioventricular block (AVB) in symptomatic patients and in asymptomatic patients with any of the following risk conditions: ventricular dysfunction, prolonged QTc interval, complex ventricular ectopy, wide QRS escape rhythm, ventricular rate lesser than 50 bpm, ventricular pauses greater than three-fold the cycle length of the underlying rhythm; 2) postoperative advanced second degree or complete AVB persisting more than 10 days; and 3) symptomatic sinus node disease, including Brady-Tachy Syndrome, when a correlation between symptoms and bradycardia is judged to be established. There are, as well, other less clear indications (Class II) to consider such as 1) asymptomatic patients with high degree and complete AVB in absence of the risk conditions mentioned previously; 2) persistent, asymptomatic post-surgical bifascicular block (with or without PR prolongation) associated with transient, complete AVB; and 3) asymptomatic resting heart rate lesser than 40 bpm or ventricular pauses lasting longer than 3 sec. Some differences can be observed when comparing the 2013 ESC Guidelines(2) to the 2012 ACCF/AHA/HRS Focused Update Incorporated Into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities(3), mainly the addition of two class IIa indications: 1) Permanent pacemaker (PM) implantation is reasonable for patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of atrioventricular (AV) synchrony; and 2) Permanent PM implantation is reasonable for unexplained syncope in the patient with prior congenital heart surgery complicated by transient complete heart block with residual fascicular block after a careful evaluation to exclude other causes of syncope. Other minor differences are the time limit to consider a postoperative AVB (7 days) and the lower limit for ventricular rate in congenital AVB (55 bpm if younger than 1 year of age or 50 bpm if older).

Often times, the choice between epicardial or endocardial PM is based on the presence of concomitant heart surgery, complex congenital defects which hinder venous access or cause intracardiac right to left shunts, history of thromboembolic disorders, small patient and consequently vessel size, surgeon preference, center experience and parental consent for a more invasive surgery. In spite or because of all these recognized influential factors, there is not a clear and established guideline to help make this choice simpler for practitioners.

Such is the case regarding the decision on which pacing mode should be applied at initial PM implantation: it depends largely on the indication for its implantation, however there is still much disagreement on whether, parting specific indications, initial dual chamber PM is the right choice or if it should be postponed given that most of these children will be PM-dependent for the rest of their lives. Although not mentioned in the 2013 ESC Guidelines(2), the 2012 ACCF/AHA/HRS Focused Update(3) suggests an initial pacing mode according to the indication for PM implantation. For AVB, a dual-chamber PM is the best choice. However, in the presence of tachyarrhythmias or if AV synchrony is not a concern another option is the single-chamber ventricular PM. Moreover, if AV synchrony is a priority but there is also a need to limit the number of PM leads implanted, a single-lead atrial sensing ventricular pacing system may be the best option. On the other hand, for sinus node dysfunction (SND), a single-chamber atrial PM it is the main choice when there isn't any suspicion of an atrioventricular conduction anomaly or risk of future development of AVB. These guidelines also present single-chamber ventricular PM as an alternative pacing mode for SND.

Like with all procedures, there are always possible complications and although some of these are procedure-dependent, others relate to the population being intervened. Owning to their condition as children, some factors ought to be considered such as small size (including vessel size), rapid growth and sudden, varied and continuous movement. Also, because, as mentioned before, children are a particular group that will probably need cardiac pacing for all of their lives, we have to look at the long-term complications that otherwise may not even manifest.

Since there is a lack of clearly defined guidelines created for children and focusing on all the particularities related not only to their small dimensions, rapid growth rate, active lifestyle and long-term pacing duration but also to the frequently associated congenital malformations, that this systematic review means to appraise the available literature on 1) the indications for cardiac pacing; 2) the most adequate type of artificial cardiac PM (epicardial vs. endocardial) according to patient characteristics; 3) the pacing mode (single-chamber vs. dual-chamber) better suited for each indication and 4) the most common complications associated with these types of cardiac implantable devices.

IV. METHODS

We conducted a systematic review pertaining to the following questions: 1) What are the current most frequent indications for artificial cardiac pacing in children?; 2) Which type of cardiac pacing is more appropriate in pediatrics, epicardial or endocardial?; 3) Which pacing mode (single chamber vs. dual chamber) is better suited for each indication?; and 4) What are the short-, medium- and long-term complications associated with each type of pacing?.

For this, we considered our PICO to be: all children aged 0 to 18 years old (Population), implanted with an artificial cardiac pacemaker (Intervention) and compared epicardial vs. endocardial devices and single vs. dual chamber systems (Comparison), later assessing pacemaker-related mortality, rate of adverse events, complications, freedom from lead failure, rate of symptom-free patients, and rate of recovery of sinus rhythm (Outcomes).

We searched MEDLINE®, EMBASE®, Web of Science, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register) and ClinicalTrials.gov, for original articles written in English or Portuguese, published from 01/01/2000 to 12/31/2018 by using the appropriate MeSH controlled vocabulary (with some adaptations when needed) in combination with database-specific filters when available.

In regard to the MEDLINE® database we used the following search equation: (pacing[Title/Abstract] OR pacemaker*[Title/Abstract]) AND (child*[Title/Abstract] OR pediatric*[Title/Abstract]) and applied the resulting search limits: publication dates from 01/01/2000 to 12/31/2018; articles written in English and Portuguese; ages between 0 and 18 years old; clinical study, clinical trial, comparative study, controlled clinical trial, evaluation study, multicenter study, observational study, periodical index, pragmatic controlled trial, randomized clinical trial, twin study and journal articles as article types. For the remaining databases, we used the same archetype with some adaptations when necessary.

Studies were then selected independently according to full-text availability, excluding reviews, case reports, age at PM implantation older than 18 years old, references to temporary pacing systems, comparisons between different lead characteristics, pacing sites and beat-to-beat capture mode, plus comparisons between patients with and without implanted pacemaker systems.

Data from the selected articles were retrieved using a template in the form of an Excel sheet as to allow for easier interpretation and none of the authors was contacted for further clarification. We sought data on the following variables: 1) Study characteristics: study design, if it was a multicenter study, time period covered by the study, follow-up protocol and duration, loss of follow-up, censoring pattern and if there were any factors controlled for; 2) Population

characteristics: final number of participants, sex, race, age and weight at implantation, presence of congenital heart defects (including dilated and hypertrophic cardiomyopathies), history of previous heart transplant, cardiac surgery or PM implantation; 3) Indications for PM implantation; 4) Intervention features: type of PM implanted, how the choice was made, what was the surgical or venous approach, if there was simultaneous cardiac surgery, location of generator pouch, mode of implanted PM, use of beat-to-beat capture mode, number, type and position of used leads, presence of an intra-atrial loop, number of PM replacements, relocations and explantations, number of upgrades and switches of PM type, data on battery depletion, lead replacements, extractions, abandonments and advancements and heart function (including left ventricular end-diastolic diameter, left ventricular ejection fraction and shortening fraction); 5) Complications, including early (less than 3 months) and late complications: pneumothorax, hemothorax, pericardial effusion (including cardiac tamponade), cardiac perforation, hematomas, wound necrosis, dehiscence or erosion, wound, pocket or lead infection and endocarditis, PM migration, abdominal hernia at pocket location, lead/PM replacement due to advisory, intervention-related lead damage, lead dislodgement, passage of lead through a patent *foramen ovale* to the left ventricle, lead straightening, lead damage/fracture, insulation defects, increased excitability threshold (including exit block), sensing anomalies (including loss of capture), battery depletion before end-of-life, tricuspid regurgitation, other valve regurgitation, muscle overstimulation (most commonly pectoral or diaphragmatic), thrombosis and venous occlusion, atrioventricular desynchrony, pacing-induced dilated cardiomyopathy and other complications; 6) Outcomes: if there were any complications related to the procedure, rate of re-interventions as well as months to re-intervention and risk factors, freedom from re-intervention rate, survival of original lead, freedom from lead failure, rate of asymptomatic patients, rate of adverse events, overall mortality, PM-related mortality, rate of patients that underwent heart transplant, sinus rhythm recovery (including good escape rhythm) rate; 7) Bias risk: selection bias (including random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and any limitations mentioned by the authors.

Variables were compared and the results were compiled and then interpreted.

Assessment of bias risk was done individually for each study according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0C(4).

V. RESULTS

Through our research equation and after gathering all relevant articles in the before mentioned databases, 964 records were identified. Of these, 44 were duplicates and therefore excluded. 920 articles were then screened to suit the research question with 799 being outright excluded for not fitting the inclusion criteria or for full-text unavailability. At that point, 121 full-texts were appraised with 85 being excluded due to the following reasons: age at PM implantation older than 18 years old, focus on etiology with few results involving pacing proper, references to temporary pacing systems, peri-operative factors of heart surgery, prophylactic placement of PM leads or the acute hemodynamic effects of PM, comparisons between different lead types, beat-to-beat capture mode and different pacing sites, and main focus being the comparison between patients with and without implanted PM systems (Figure 1).

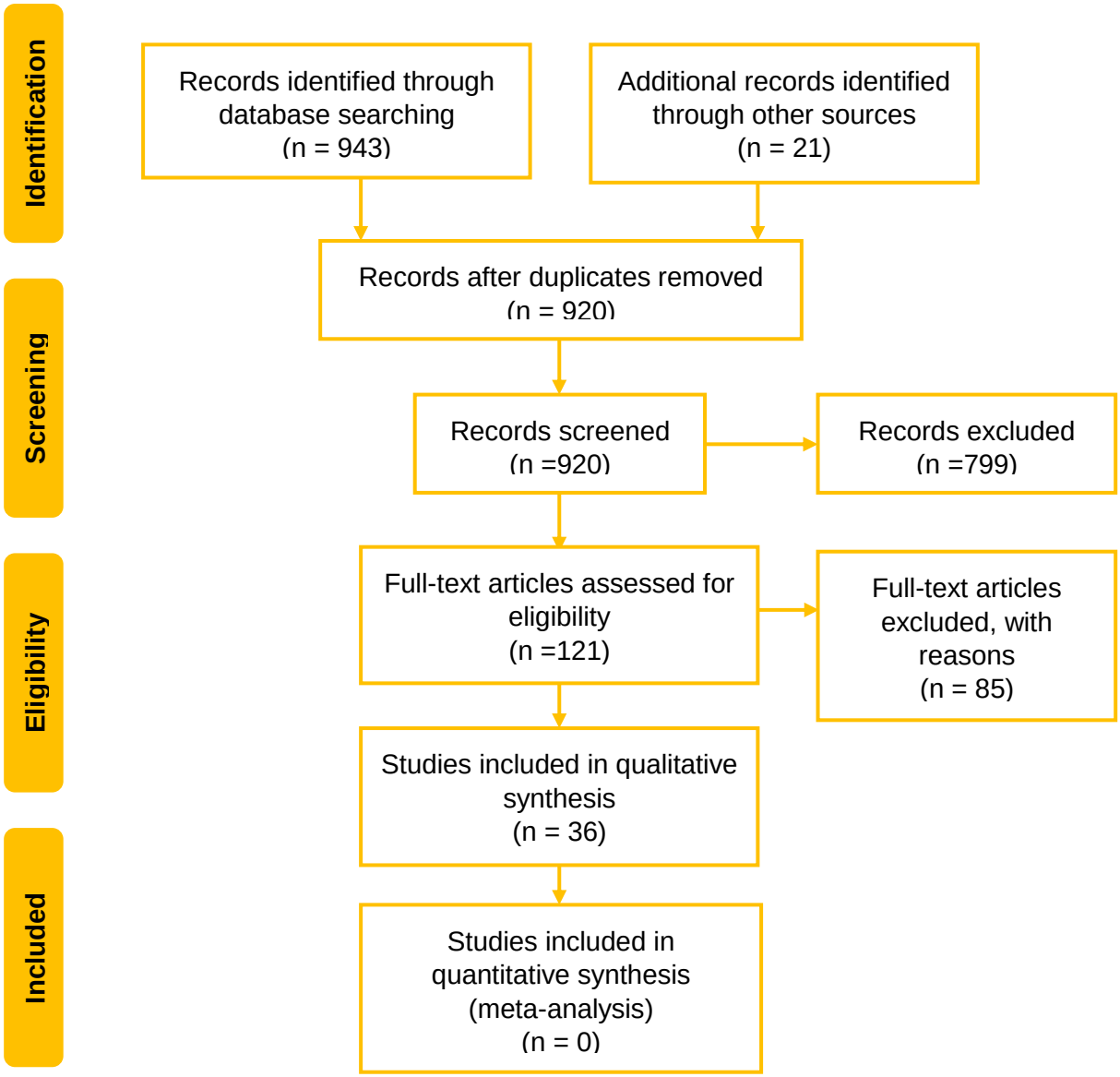

Figure 1: PRISMA® Out-Flow Diagram

Tables IA, IB and IC show us the citations for the selected articles as well as major study characteristics, number of paper citations as stated in Web of Science and the publication journal's SJR Ranking.

In Tables IIA through IIH we can see each individual study's PICOs, conclusions drawn, and study limitations as mentioned by the authors.

Out of the 36 selected studies, only 3 provided the indications for the procedure: Kammeraad 2004(5) mentions heart failure and bradycardia and isolated heart failure, failure to thrive, syncope, cardiac enlargement, isolated bradycardia, runs of more than 3 ventricular extrasystoles and an increase in QT interval); Beaufort-Krol 2007(6) mentions symptomatic congenital sinus node disease, bradycardia, long-pause and dilated cardiomyopathy; Balmer 2002(7) mentions heart failure, exercise intolerance, bradycardia and unexplained syncope. The other 34 studies referred to etiology to justify the PM implantation. Among these, 3 studies mentioned that indications followed ESC(2) or ACCF/AHA/HRS(3) guidelines but did not specify which indications merited the implantation procedure. For etiology the numbers in were as follows: 579 congenital AVB, 145 congenital and acquired AVB, 679 post-operative AVB, 87 AVB (not specified), 46 congenital SND, 20 post-operative SND, 2 acquired SND, 195 SND (not specified), 22 congenital AVB and SND, 162 post-operative AVB and SND, 10 Long-QT Syndrome, 110 other and 127 not mentioned.

Nine studies refer to endocardial PM implantation, 17 to epicardial, 8 compare endocardial and epicardial PM implantation, 1 focuses on left ventricle (LV) function independently of the type of PM(6) and 1 refers to the impact of PM implantation independently, once again, of the type of PM(7).

Nine studies mention specific pacing modes; however, none directly compare them with either each other or with a control group.

Mentioned complications are as follows: pneumothorax, hemothorax, pericardial effusion, cardiac perforation, hematomas, wound necrosis/dehiscence/erosion, wound/pocket/lead infection, mediastinitis, sensing anomalies, loss of capture, increased pacing threshold, exit block, lead damage/fracture, intervention-related lead damage, lead/PM removal as per advisory, insulation defects, earlier depletion of battery-life than anticipated, lead displacement, lead under traction due to somatic growth, lead passing through a patent *foramen ovale*, AV valve regurgitation, PM migration, abdominal hernia at PM site, muscle stimulation, abdominal irritability/pain due to overstimulation, phrenic nerve palsy, PM-induced tachycardia, atrial flutter and atrial and ventricular fibrillation.

Pacemaker-related mortality was mentioned by 26 out of 36 studies: most of said studies state that no deaths occurred related to PM use; all those who do - 6 studies(7–12) -,

mention 1 death with two exceptions where there is mention of 2 deaths(9,11). These deaths were related to sensing anomalies, exit block or sudden deaths with exclusion of other causes.

Rate of adverse events was mentioned by only 3 out of 36 studies: Zhang 2016(1) mentions events in 7 patients (7 out of 35) all with complex congenital heart disease (CHD); Toralles 2014(12) mentions freedom from adverse events as 94.1%±4 at 3m, 91.2%±4.9 at 18m and 34.2%±6.5 at 36m with lower percentages for patients with previous cardiac surgery (however, the correlation was not statistically significant) and Balmer 2002(7) mentions 1 (1 out of 26) adverse event.

Freedom from lead failure was analyzed in 9 studies: Tomaske 2008(13) (epicardial PM implantation) mentions 99% and 94% at 2 and 5 years, respectively, for atrial leads and 96% and 85% at 2 and 5 years, respectively, for ventricular leads; Lau 2015(9) (epicardial PM implantation) mentions 99%, 93%, 83% and 72% at 1, 2, 5 and 10 years, respectively, for atrial leads and 97%, 90%, 74% and 60% at 1, 2, 5 and 10 years, respectively, for ventricular leads; Murayama 2007(14) (epicardial PM implantation) mentions 100%, 89%, 72.5%, 55.5% at 1, 5, 10 and 15 years and that associated structural heart disease was the only significant predictor for lead failure ($p=0.011$); Kubus 2012(10) (epicardial PM implantation) mentions 94% and 58.3% at 8 years for bipolar and unipolar leads respectively ($p<0.001$), higher freedom from exit block at 95.3% and 76.2% for SE leads versus non-SE leads ($p<0.001$), and finally a $p=0.028$ per each 10cm increasement in height at implantation as a multivariable predictor; Thomson 2004(15) (epicardial PM implantation) mentions an overall freedom form lead failure of 87%, 81% and 66% at 1, 2 and 5 years, with better results for steroid-eluting (SE) leads (92% at 1 year, 86% at 2 years and 76% at 5 years) than non-SE leads (77% at 1 year, 73% at 2 years and 50% at 5 years); Brzezinska-Paszkee 2006(16) (epicardial PM implantation) mentions that at last follow-up 39 patients with SE leads (53 patients in total) still had their first leads and that for non-SE leads (29 patients in total) only 18 patients still had their first leads; Cate 2002(17) (epicardial vs. endocardial PM implantation) mentions that the only difference found between epicardial and transvenous leads was for weight at first implantation ≤15Kg with epicardial leads requiring a greater number of reinterventions; Kwak 2012(18) (epicardial PM implantation) mentions 98.3%, 91.6%, 83.5% and 63.3% at 1, 2, 5 and 10 years with lead longevity shorter for those less than 1 year old at first implantation; Silvetti 2006(19) (epicardial vs. endocardial PM implantation) mentions 21% lead failure for epicardial leads and a 6% lead failure for transvenous leads ($p<0.05$) .

Risk factors for re-intervention were identified through 8 studies: Noiseux 2004(8) (epicardial PM implantation) states that any indication other than AVB is a risk factor and that the execution of a sternotomy is the only independent risk factor; Lau 2015(9) (epicardial PM implantation) refers to age at first implantation, gender, single ventricle status and implantation

in earlier years as risk factors; Murayama 2007(14) (epicardial PM implantation) associates age at first implantation, gender, prior heart surgery and especially CHD with lead failure; Papadopoulos 2010(20) and Bakhtiary 2007(21) (both addressing epicardial PM implantation) refer to PM pocket abdominal location with the crossing between the pericardial cavity and the abdominal wall, where the diaphragm works as a hinge point, as a risk factor for lead damage and consequent need for re-intervention; Kubus 2012(10) (epicardial PM implantation) states that the use of unipolar leads constitutes a risk factor; Thomson 2004(15) (epicardial PM implantation) talks about the implantation of non-SE leads and implantation in earlier years as risk factors; and, Silvetti 2007(22) (endocardial PM implantation) refers to the absence of creation of an atrial loop during transvenous system's implantation as a risk factor.

Only 3 out of 36 studies mention rate of symptom-free patients: De Filippo 2018(23) mentions 36/40 (90%), Vos 2016(24) mentions 7/7 (100%) and Balmer 2012(7) mentions 26/26 (100%) symptom-free patients.

Rate of recovery of sinus rhythm is mentioned by 10 studies: Kammeraad 2004(5) mentions 3/39 (8%), Konta 2016(25) mentions 1/37 (3%), Vos 2016(24) mentions 0/7 (0%), Südkamp 2004(26) mentions 0/12 (0%), Noiseux 2004(8) mentions 0/122 (0%), Papadopoulos 2010(20) mentions 0/45 (0%), Kwak 2012(18) 3/53 (6%), Lotfy 2012(27) mentions 3/91 (3%) -all post-operative AVBs-, Silvetti 2006(19) mentions 1/292 (0,3%) and Aellig 2007(28) mentions 1/22 (5%).

Assessment of individual bias risk, as per the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0C(4), can be seen in Table III.

Table IA: Study Characteristics

Nº	Article	Author	Year	Multi-centre	Study Design	Time Period	Study Size	Follow-Up Duration (mean)	Paper Citations	Journal SJR (Quartile, Ranking)
1	Single-pass lead VDD pacing system in children and adolescents: report of twenty-four patients	Çeliker, A	2006	No	NM	1994-2004	24	7m-84m	1	0.404 (Q3, 202)
2	Transvenous pacing in pediatric patients with bipolar lumenless lead: Ten-year clinical experience	De Filippo, P	2018	No	Prospective	2006-2016	40	0.9y-10.8y (6±2.9y)	NA	1.200 (Q1; 78)
3	Transvenous pacing in children weighing less than 10 kilograms	Robledo-Nolasco, R	2009	No	Retrospective	2001-2008	12	31.8±23.5m	9	1.028 (Q2; 94)
4	Endocardial pacemaker implantation in infants weighing ≤10 kilograms	Kammeraad, J. A. E.	2004	Yes	Retrospective	1987-2002	39	9m-15.3y (4.3y)	42	1.028 (Q2; 94)
5	Twenty-seven years' experience with transvenous pacemaker implantation in children weighing <10 kg	Konta, L	2016	No	Retrospective	1987-2003	37	11.2-27.4y (17.2y)	3	3.225 (Q1; 22)
6	Long-term outcome of transvenous pacemaker implantation in infants: a retrospective cohort study	Vos, L.M.	2016	No	Retrospective	1997-2001	7	12.3y-16.3y (median 14y)	2	2.748 (Q1; 25)
7	Outcomes of long-term endocavitary cardiac pacing in children	Szklarz, E	2013	No	Retrospective	1999-2012	106	12y	NA	0.215 (Q3;252)
8	VDD-pacemaker in children - a long-term therapy?	Südkamp, M.	2004	No	Retrospective	1977-2001	12	47.5±15.1m	NA	NA
9	A 12-year experience of bipolar steroid-eluting epicardial pacing leads in children	Tomaske, M	2008	No	Prospective	1994-2006	114	0.1y-12.2y (3.2y)	42	1.294 (Q1; 71)
10	Thirty years of experience with epicardial pacing in children	Noiseux, N	2004	No	Retrospective	1971-2001	122	1d-21.2y (6.4±4.7y)	18	0.372 (Q3; 211)
11	Long-term atrial and ventricular epicardial pacemaker lead survival after cardiac operations in pediatric patients with congenital heart disease	Lau, K.C.	2015	No	Retrospective	1984-2010	155	SV: 5.7y, IQR 2.9-9.4; BiV 3.7y IQR 0.8-9.1	9	3.231 (Q1; 21)
12	Predictors affecting durability of epicardial pacemaker leads in pediatric patients	Murayama, H	2007	No	Retrospective	NM	55	3d-22.9y (6.4y)	17	2.297 (Q1; 35)

NM: not mentioned; m: months; y: years; IQR: Inter-Quartile Range; Q: Quartile

Table IB: Study Characteristics

№	Article	Author	Year	Multi-centre	Study Design	Time Period	Study Size	Follow-Up Duration (mean)	Paper Citations	Journal SJR (Quartile, Ranking)
13	Long-term follow-up after steroid-eluting epicardial pacemaker implantation in young children: a single centre experience	Papadopoulos, N	2010	No	Retrospective	2000-2008	45	6m-7.3y (5.7y±15m)	12	2.748 (Q1; 25)
14	Medium-term follow-up and modes of failure following epicardial pacemaker implantation in young children	Bakhtiary, F	2007	No	Prospective	2000-2005	21	Up to 61m (41.2m)	9	2.748 (Q1; 25)
15	Permanent epicardial pacing in children: long-term results and factors modifying outcome	Kubus, P	2012	No	Retrospective	1977-2009	119	6.4y (IQR 2.9-11.1)	22	2.748 (Q1; 25)
16	Pacing activity, patient and lead survival over 20 years of permanent epicardial pacing in children	Thomson, J.D.R.	2004	No	Retrospective	1980-2001	59	1.1-22y (11.9)	25	1.294 (Q1; 71)
17	Steroid-eluting epicardial pacing in children	Brzezinska-Paszkee, M	2006	No	Retrospective and Prospective	1989-2004	82	I: 1w-7.3y (2.5y); II: 2m-15y (7.7y)	NA	NA
18	Endocardial and epicardial steroid eluting lead pacing in the neonatal and paediatric age group	ten Cate, F.U.	2002	Yes	Retrospective	1990-2000	95	A: T 2y±1, E 2.4y±2.2; B: T 2.1y±1.9, E 2.8y±1.3	NA	2.853 (Q1; 24)
19	Risk factors for complications in the implantation of epicardial pacemakers in neonates and infants	Chaouki, A.S.	2017	No	Retrospective	1996-2015	86	<1y	3	3.231 (Q1; 21)
20	Permanent epicardial pacing in pediatric patients: 12-year experience at single center	Kwak, J.G.	2012	No	Retrospective	1997-2009	53	2.1m-17y (8±4.5)	17	1.294 (Q1; 71)
21	Surgical placement of permanent epicardial pacing systems in very low-birth weight premature neonates: a review of data from the pediatric cardiac care consortium (PCCC)	Shepard, C.W.	2012	Yes	Retrospective	1982-2006	10	NM	3	0.407 (Q3; 200)
22	Single chamber permanent epicardial pacing for children with congenital heart disease after surgical repair	Zhang, T	2016	No	Retrospective	2002-2014	35	46.8m±33.8	3	0.607 (Q2; 157)
23	Twenty years' experience with pediatric pacing: epicardial and transvenous stimulation	Sachweh, J.S.	2000	No	Retrospective	1979-1998	71	1m-12.9y (3.2y±4)	93	NA
24	Equivalent performance of epicardial versus endocardial permanent pacing in children: a single institution and manufacturer experience	Odim, J	2008	No	Retrospective	1990-2003	160	T <110m (32.5±29.3); E <89m (23.9±22.8)	19	1.294 (Q1; 71)
25	Single-centre experience on endocardial and epicardial pacemaker system function in neonates and infants	Silvetti, M.S.	2007	No	Retrospective	1992-2004	56	3m-13y (4.5y±3.5, median 4y)	30	2.748 (Q1; 25)

NM: not mentioned; m: months; y: years; IQR: Inter-Quartile Range; Q: Quartile; T: Transvenous; E: Endocardial

Table IC: Study Characteristics

№	Article	Author	Year	Multi-centre	Study Design	Time Period	Study Size	Follow-Up Duration (mean)	Paper Citations	Journal SJR (Quartile, Ranking)
26	Longitudinal echocardiographic follow-up in children with complete congenital atrioventricular block	Beaufort-Krol, G.	2007	No	Prospective	1976-?	17	NM	12	1.028 (Q2; 94)
27	Late results with permanent cardiac pacing in children less than two years of age	Toralles, EK	2014	No	Retrospective	1997-2010	34	5-160m (60,5m)	NA	NA
28	Long-term follow up of children with congenital complete atrioventricular block and the impact of pacemaker therapy	Balmer, C	2002	No	Retrospective	1980-1997	26	0.3-20y (median 10.2y)	30	2.748 (Q1; 25)
29	Complications and risk assessment of 25 years in pediatric pacing	Wilhelm, BJ	2015	No	Retrospective	1985-2010	73	7.9y	8	1.294 (Q1; 71)
30	Permanent pacing in infants and children: a single center experience in implantation and follow up	Samir, R	2011	No	Prospective	1996-2010	32	0.25-14y (median 2.5y)	NA	0.160 (Q4; 277)
31	Permanent Cardiac Pacing in Pediatric Patients	Lofty, W	2012	No	Cross-sectional	2001-2010	91	7.16y	NA	0.830 (Q2; 119)
32	Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients	Silvetti, M.S.	2006	No	Retrospective	1982-2002	292	1m-18y (5y±4)	71	2.748 (Q1; 25)
33	Outcome of single-chamber, ventricular pacemakers with transvenous leads implanted in children	Silvetti, M.S.	2007	No	Retrospective	1990-2005	117	1y-15y (7.8y±4.1, median 8y)	15	2.748 (Q1; 25)
34	The development of pacing induced ventricular dysfunction is influenced by the underlying structural heart defect in children with congenital heart disease	Balaji, S.	2017	Yes	Retrospective	2005-2014	47	NM	1	0.333 (Q3; 219)
35	Long-Term follow-up after pacemaker implantation in neonates and infants	Aellig, NC	2007	No	Retrospective	1992-2004	22	0.01y-12.8y (4.6y)	22	1.294 (Q1; 71)
36	Left ventricular pacing in neonates and infants with isolated congenital complete or advanced atrioventricular block: short- and medium-term outcome	Silvetti, M.S.	2015	No	Prospective	2010-2012	10	At least 12m	10	2.748 (Q1; 25)

NM: not mentioned; m: months; y: years; IQR: Inter-Quartile Range; Q: Quartile

Table IIA: Individual Study Results

	PICOS	Conclusions	Limitations (mentioned by the authors)
1	AV synchrony in single pass lead VDD transvenous PM implantation in 24 children and adolescents between 1994 and 2004	Low complication rate. VDD can be used successfully in children with congenital complete AVB and normal sinus function. Patient and lead selection should be taken under consideration for the maintenance of AV synchrony.	
2	Long-term safety and efficacy of the endocardial device implantation technique used in 40 paediatric patients under 16 years old from 2006 to 2016.	The use of Select Secure™ lead, together with the choice of axillary vein access, the creation of an intra-atrial loop of the leads and the placement of the generator in a sub-pectoral pocket, can reduce complication rate and ensure a safe and effective stimulation, up to 10 years of follow-up (average 6 ± 2.9 years). Recent certification of Select Secure™ lead as MRI-compatible could increase the use of this lead in children and young patients.	Retrospective study. Single cardiac centre, where physicians are experts at cardiac device implantation in paediatric patients and familiar with the Select Secure™ lead. Lack of comparison between Select Secure™ and conventional PM leads.
3	Endocardial PM implantation, from 2001 to 2008, in 12 infants weighing <10Kg.	Endocardial implantation of permanent PMs in children weighing <10Kg was feasible. Improvements in the design and smaller generators and leads allow the use of transvenous pacing systems in this patient population. A subclavian venogram and progressive dilation of the vein facilitate the lead placement and lower the risk of vascular complications.	
4	Endocardial PM implantation, from 1987 to 2002, at two different centres in 39 children weighing ≤10Kg.	Endocardial pacing in small children is feasible and effective. It is an acceptable alternative to epicardial PM implantation. Use of the smallest available leads and on-going developments in this area are likely to make endocardial pacing more widely acceptable. At present, the final choice of an endocardial or epicardial approach in children ≤10Kg in weight should be based on the experience and expertise available in the unit treating these patients	
5	Long-term report of transvenous pacing implantation between 1987 and 2003 in 37 patients weighing under 10Kg followed up for a minimum of 11 years.	Transvenous pacing has an encouraging long-term outcome in infants weighing <10Kg, with documented venous patency at up to 25 years and original lead survival up to 17.6 years. Weight <5Kg appears to be a risk factor for subclavian vein occlusion, while occlusion in those weighing 5–10Kg was similar to that in older paediatric patients. Although epicardial approach is standard, a single lead transvenous pacing system can be implanted in infants when an open surgical procedure is not optimal.	

AVB: Atrioventricular block; AV: Atrioventricular; PM: Pacemaker

Table IIB: Individual Study Results

	PICOS	Conclusions	Limitations (mentioned by the authors)
6	Long-term outcome of transvenous PM implantation in 7 infants weighing <10Kg between 1997 and 2001.	Transvenous PM implantation in infants (<10Kg) is associated with a high incidence of vascular occlusion, thrombosis, and severe atrioventricular valve regurgitation during long-term follow-up. We advocate an epicardial approach for PM implantation in small children.	
7	Long-term follow-up in 106 children undergoing permanent transvenous pacing therapy between 1999 and 2012.	Transvenous PM implantation in children is a minimally invasive method, feasible for use even in small children. In long-term follow-up, it is associated with a low risk of unfavourable clinical consequences resulting from this method of pacing.	
8	Long-term outcome of single lead VDD transvenous pacing implantation in 12 children <15 years old between 1977 and 2001	In small children with normal sinus function, VDD PMs can be safely implanted with a low complication rate perioperatively. However, in the long-term it seems to be a temporary solution to bridge AV synchrony from young age to DDD pacing in young adulthood.	
9	Pacing and sensing characteristics, of bipolar steroid-eluting epicardial pacing leads in 114 patients implanted between 1994 and 2006.	Bipolar steroid-eluting epicardial leads demonstrate excellent sensing characteristics and persistent low median pacing thresholds in children during up to 12 years follow-up. Considering growing and active patients with most having CHD, the lead survival of 85% to 94% at 5 years is favourable.	Use of different devices with slightly different threshold and R-wave measurements.
10	Long-term safety of epicardial PMs implanted in 122 children between 1971 and 2001	Epicardial pacing is a reliable means of achieving permanent pacing in children, with low morbidity and mortality. A substantial proportion requires reintervention within five years, warranting meticulous follow-up to ensure adequate margins of safety for threshold, anticipate need for changes in the generator, screen for PM malfunction, and to optimize programmable settings.	
11	Long-term lead survival, morbidity and mortality in 155 paediatric patients with CHD who had epicardial lead placement in association with surgical repair or palliation between 1984 and 2010	Epicardial leads had acceptable longevity despite cardiac operations for complex CHD, suggesting the long-term reliability of this pacing method.	Retrospective, single-centre study Small sample size Large number of losses to follow-up or interventions at other institutions. Lack of comparison with transvenous lead placement.

Table IIC: Individual Study Results

	PICOS	Conclusions	Limitations (mentioned by the authors)
12	Long-term outcomes and predictors affecting lead durability in 55 paediatric patients undergoing epicardial pacing therapy over a 20-year period	Epicardial leads provide a reliable technique for managing rhythmic disturbance problems in the paediatric population. The only significant predictor of lead failure is the presence of structural CHD	Retrospective study. Choice of lead varied with technical development over time. Small number of leads.
13	Long-term results of single and dual-chamber PMs and bipolar, steroid-eluting epicardial leads in 45 children between 2000 and 2008. Clinical outcome and modes of failure leading to reoperation in children who underwent epicardial PM implantation.	Epicardial pacing in young children was associated with a satisfactory clinical outcome and acceptable long-term results. A significant number of failures leading to reoperation occurred in our patient cohort: despite the stable pacing and sensing parameters during long-term follow-up, electrode fractures were caused by the muscular activity of this patient group. Reoperations could be performed at a low risk.	Lack of comparison with transvenous leads. Patient selection. Inability to provide AV synchronous pacing in all patients because of the need for a larger thoracotomy not consented by the patient's legal guardian.
14	Medium-term results of single- and dual-chamber PMs and bipolar, steroid-eluting epicardial leads in 21 children between 2000 and 2002. Clinical outcome and modes of failure leading to reoperation in children who underwent epicardial PM implantation.	Overall good clinical outcome. Epicardial pacing in young children was associated with a significant number of failures leading to reoperation, mainly due to electrode fracture caused by muscular activity. Reoperations were performed at a low risk. Dual chamber PM implantation was feasible even in very small infants with a low perioperative complication rate.	
15	Long-term results of permanent epicardial pacing in 119 children between 1997 and 2009. Factors modifying pacing system survival.	The probability of continued epicardial pacing in children was 76% at 10 years after implantation, increased for implantation in recent years. The use of bipolar steroid-eluting leads and of a beat-to-beat capture tracking feature significantly increased pacing system longevity and decreased the need for surgical reinterventions.	Changes in technology and major differences in follow-up over time. Small number of patients with follow-up longer than 11 years. Data on the clinical consequences of pacing-induced dysynchrony could not be amended by systemic ventricular function parameters.
16	Paediatric epicardial pacing activity, patient and lead survival in 59 children between 1980 and 2001.	Epicardial approach is an effective solution. Lead survival has improved with more than 75% of steroid eluting leads surviving to 5 years. The only statistically significant predictor of lead survival other than steroid eluting lead technology was decade of implant.	

PM: Pacemaker

Table IID: Individual Study Results

PICOS		Conclusions	Limitations (mentioned by the authors)
17	Pacing characteristic and follow-up of 53 children implanted with epicardial steroid-eluting pacing leads between 1989 and 2004.	The pacing thresholds of steroid-eluting leads are significantly lower than those of non-steroid-eluting leads. The pacing threshold of ventricular steroid eluting leads increases throughout the several years of follow-up, while the pacing threshold of atrial steroid-eluting leads remains stable.	
18	Multicentre review between 1990 and 2000 comparing performance and longevity of steroid eluting epicardial and endocardial leads in 95 children requiring permanent PM.	Endocardial and epicardial steroid eluting leads have comparable performances. Higher incidence of complications associated with epicardial pacing. Epicardial pacing in smaller children with preservation of the veins for later use appears to be a rational approach.	Institutional bias in the choice of pacing with epicardial systems in younger patients. Differences in the choice of generator. Most epicardial leads were unipolar, whereas 83% of endocardial leads were bipolar.
19	Patient and device characteristics in 86 children younger than 1 year of age implanted with an epicardial PM between 1996 and 2015	Young age and low weight at the time of implantation are risk factors for complications, while device characteristics seem to appear to play a minor role. Reserving PM implantation for patients >3Kg in weight and 5 days of age may predict patients at low risk of developing complications	Retrospective, single centre study. Selection bias. Loss of follow-up. Younger and lower weight patients may represent a group who are associated with confounding variables. Possible underestimation of complication rate. Morbidity and mortality secondary to bradycardia in patients waiting to achieve requisite size and age could not be assessed. The effect of pocket burden from leads could not be assessed, as lead type and length were not documented for all patients.
20	12-year experience (from 1997 to 2009) and outcomes of the implantation of epicardial PMs in 53 paediatric patients	Epicardial cardiac pacing is an effective and appropriate treatment for paediatric patients. Epicardial leads had excellent longevity whether of the steroid-eluting type or not. Generators implanted in younger patients tended to show early exhaustion; however, this was not statistically significant and so, generator longevity was not affected by lead type, generator mode, or patient age at the time of PM implantation.	
21	Mortality and morbidity associated with early placement of a permanent epicardial PM for CHB in 10 low-birth weight infants identified in a large multicentre database (1982 to 2006)	Permanent PM placement should be considered for the initial procedure in those without structural heart disease. We suggest placing both ventricular and atrial leads when clinically indicated by hemodynamic instability. Low-birth weight infants with CHB and congenital cardiac defects remain an exceptionally high-risk population in need of further investigation.	

CHB: Congenital Heart Block; PM: Pacemaker

Table IIE: Individual Study Results

	PICOS	Conclusions	Limitations (mentioned by the authors)
22	10-years' experience (from 2002 to 2014) in placement of single-chamber permanent epicardial PM and its mid-terms outcomes in 35 children with CHD	High-degree iatrogenic atrioventricular block was the primary reason for placement of epicardial PM for patients with CHD after surgical repair. PM placement with the steroid-eluting leads results in acceptable outcomes, however, the PM type should be optimized for children with complex CHD.	
23	20-years' experience (from 1979 to 1998) in epicardial and transvenous pacing implantation in 71 children	Transvenous pacing in the paediatric population is associated with a lower acute stimulation threshold and a lower rate of lead-related complications. If epicardial pacing is necessary (e.g. small body weight, special intracardiac anatomy, impossible access to superior vena cava), steroid-eluting leads may be the best choice.	
24	Mortality, freedom from lead failure and PM system reintervention of steroid-eluting epicardial and endocardial pacing leads in 148 children from 1990 to 2003.	Steroid-eluting epicardial pacing leads appear as safe and proficient as their endocardial counterparts in children. In light of expanding indications for pacing, biologic constraints of growing children, and limited endovascular domain, consideration of epicardial pacing systems remain an attractive alternative strategy	Retrospective study with inability to obtain complete record. Complications related to transvenous systems may remain asymptomatic and undetectable in the absence of routine angiography or echocardiography
25	12-years' experience (from 1982 to 2004) with PM implantation in 56 neonates and infants	Endocardial pacing is feasible and shows good results in experienced centres, even in infants. In this group of patients with thin transvenous leads, no venous occlusion was found during follow-up. The efficacy and safety with the current available medium-term follow-up indicate that single-lead, VVIR endocardial pacing is probably the best choice outside the neonatal period.	Retrospective, single-centre study. Institutional bias in the choice of pacing system in the years of 2000 to 2004. Loss of follow-up. Small sample size. Venous patency was only examined in 13 of 16 patients with endocardial pacing and only through a non-invasive method. Some pacing parameters were not always recorded. Lack of longer follow-up. Evolution of pacing generators and leads' technology.

CHD: Congenital Heart Disease; PM: Pacemaker

Table IIF: Individual Study Results

PICOS		Conclusions	Limitations (mentioned by the authors)
26	Evaluation by serial echocardiography of the effects of PM therapy on LV dilation in 44 children with CCAVB without associated CHD since 1976	Children with CCAVB have LV dilatation, which is progressive in children who ultimately met criteria for PM implantation. LV dilatation regressed with physiologic pacing. LV dilatation was larger when heart rate was lower. LV function (SF) in CCAVB does not deteriorate over time. DCM in CCAVB occurs early in the disease and does not develop during childhood, not even in the children with LV dilatation. Yearly evaluate children with CCAVB with echocardiography.	Methods to study asynchrony echocardiographically are from recent years and therefore not included Echocardiographic measurements after pacing may be controversial since ventricular pacing causes intra- and interventricular mechanical dysynchrony. Small sample size The children included were diagnosed at older age than those in contemporary studies.
27	10-years' experience (from 1997 to 2010) with epicardial pacing in 34 children younger than 2 years old.	Epicardial PM implantation has satisfactory survival rates, including in those with previous heart surgery. Epicardial PM implantation deserves consideration in patients with small physical structure, those with specific cardiac malformations, and difficult access to superior vena cava or those who need to have an associated surgical procedure. Long-term follow-up is needed to evaluate possible complications and subsequent need for reintervention.	
28	Survival, morbidity and impact of PM therapy in 32 children with congenital complete atrioventricular block between the years of 1980 and 1997	PM therapy reduces mortality and morbidity when compared with natural history data. There is no significant difference between children with structurally normal hearts and children with congenital heart disease concerning frequency of symptoms and need for PM therapy. Despite some PM complications necessitating reoperation, a satisfactory battery service life was achieved.	
29	Complications and risk factors of endocardial and epicardial PM implantation from 1985 to 2010 in 73 children	Cardiac pacing is particularly challenging in the paediatric patients facing many reoperations during their lifetime. For children weighing <15Kg superiority of either epicardial or endocardial PM systems has not been established. The accurate choice of a PM system heavily depends on a variety of patient-specific factors including anatomy and advantages for each system when considering specific patient factors.	Retrospective study. Small sample size when compares to research about clinical problems with higher incidences. Impossibility of using a matched case-control design to avoid possible confounders when calculating relative risks and odds ratios

CCAVB: Complete Congenital Atrioventricular Block; DCM: Dilated Cardiomyopathy; LV: Left Ventricle; SF: Shortening Fraction; PM: Pacemaker

Table IIG: Individual Study Results

PICOS		Conclusions	Limitations (mentioned by the authors)
30	Experience in PM implantation procedures and long-term outcomes between 1996 and 2010 in 32 children	Permanent pacing in paediatric patients is generally safe and has a favourable long-term outcome. There is a high rate of complications, mainly related to leads, especially in younger and smaller children. With steroid-eluting leads, transvenous and epicardial pacing are initially comparable. In the older child or in the adolescent, endocardial pacing should be considered as the first choice	Single centre. Small sample size.
31	Indications and complications of paediatric cardiac pacing in 91 children from 2001 to 2010	Endocardial PM insertion in children is a safe procedure with less complications and a lower ventricular threshold than epicardial PM insertion. Permanent single-chamber RV pacing is safe and can lead to significant improvement in LV function and dimensions. However, long-term follow- up assessment is needed for further evaluation.	
32	Long-term outcome of PM implantation from 1982 to 2002 in 292 paediatric patients	Permanent pacing in paediatric patients is generally safe and has a favourable long-term outcome, but there remains a high rate of complications, mainly related to leads. Therefore, we suggest minimizing the number of leads implanted. Transvenous and epicardial pacing are initially comparable. However, epicardial pacing shows more long-term complications. In the older child or in the adolescent, endocardial pacing should be considered as the first choice.	
33	Outcome of VVI/R transvenous PM implantation from 1990 to 2005 in 117 children	VVI/R pacing has good results. However, at long-term follow-up there were 19% of failures, mainly lead-related. The frequency of infection and subclavian vein occlusion is low; Atrioventricular valve damage has not been demonstrated.	Retrospective, single-centre study. Small sample size. Doppler evaluation of the subclavian vein, performed in a subgroup of our patients, is less sensitive than angiography or intravascular ultrasound for vessel patency determination.

LV: Left Ventricle; PM: Pacemaker

Table IIH: Individual Study Results

	PICOS	Conclusions	Limitations (mentioned by the authors)
34	Incidence of pacing-induced ventricular dysfunction after placement of a conventional dual-chamber right epicardial PM in 47 children who developed complete AV block after surgery for CHD from 2005 to 2014	Pacing-induced ventricular dysfunction occurred in certain CHD but not others. There was no association with prolonged QRS duration. The association with RV pacing needs further study.	Retrospective study. Small sample size. It is possible that certain kinds of CHD not included are at risk of developing pacing-induced ventricular dysfunction. The CHD correction surgeries and the PM implantation surgeries were performed by different surgeons in different hospitals. The left ventricular %FS can be an unreliable measure of ventricular function in patients with dysynchrony.
35	Long-term outcomes of epicardial PM implantation in 22 children from 1992 to 2004	The outcome of PM therapy is excellent in neonates and infants, using bipolar steroid-eluting epicardial pacing leads. Sensing and pacing properties are good and remain stable over time. Lead complications or dysfunctions are rare and usually do not require reinterventions. Generator service life is acceptable, considering the complete PM dependency at high pacing rates in most of these patients.	
36	Short- and medium-term LV function and clinical status in LV epicardial PM implantation between 2010 and 2012 in 10 children	Good clinical status in all patients and normal LV function in all but one patient. Absence of interventricular dysynchrony, LV dysynchrony, and systolic dysynchrony. A reverse remodelling of LV dimensions and function in patients with LV dilatation and impaired EF at implantation QTc duration within normal limits or only slightly prolonged as compared with native complexes, most likely as a sign of electromechanical reverse remodelling.	The study was not intended to compare different pacing sites. Lack of a prospective control group. Small sample size. Short follow-up duration. Lack of a direct comparison of echocardiographic data before and after PM implantation.

AV: Atrioventricular; CHD: Congenital Heart Disease; EF: Ejection Fraction; FS: Fractional Shortening; LV: Left Ventricle; PM: Pacemaker; QTc: Corrected QT interval

Table III: Risk of Bias

Nº	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random Sequence Generation	Allocation Concealment				
1	+	+	+	+	+	-
2	+	+	+	+	-	-
3	+	+	+	+	-	-
4	+	+	+	+	-	+
5	+	+	+	+	-	+
6	+	+	+	+	-	-
7	+	+	+	+	-	+
8	+	+	+	+	+	+
9	+	+	+	+	-	-
10	+	+	+	+	-	-
11	+	+	+	+	-	-
12	+	+	+	+	-	-
13	+	+	+	+	-	+
14	+	+	+	+	+	-
15	+	+	+	+	-	-
16	+	+	+	+	-	+
17	+	+	+	+	-	+
18	+	+	+	+	-	-
19	+	+	+	+	-	-
20	+	+	+	+	+	+
21	+	+	+	+	-	-
22	+	+	+	+	-	-
23	+	+	+	+	-	-
24	+	+	+	+	-	-
25	+	+	+	+	-	-
26	+	+	+	+	-	+
27	+	+	+	+	+	+
28	+	+	+	+	-	+
29	+	+	+	+	-	-
30	+	+	+	+	-	+
31	+	+	+	+	-	+
32	+	+	+	+	-	-
33	+	+	+	+	-	-
34	+	+	+	+	-	-
35	+	+	+	+	-	+
36	+	+	+	-	-	-

VI. DISCUSSION

PACING INDICATIONS

The large majority of the studies reviewed did not expound on what indications motivated the implantation of a PM system; in those who did however, bradycardia was by far the most common indications for PM placement.

Instead of indication for implantation, the authors often referred to etiology to justify PM placement: AVB was the most frequent (with a similar number of congenital and post-operative and a much smaller number of acquired AVBs -be they post-inflammatory or associated with hypertrophic obstructive cardiomyopathy or dilated cardiomyopathy), followed by SND (firstly congenital, secondly post-operative and thirdly, and much rarer, acquired) and lastly Long-QT syndrome. Other etiologies mentioned were breath-holding spells, reflex anoxic seizures and tachyarrhythmias.

PACING TYPE: EPICARDIAL vs. TRANSVENOUS PACING

In more recent studies with the advent of SE leads and beat-to-beat capture mode(10), short-term performance between transvenous and epicardial pacing appears to have similar results(19,29,30). Nonetheless, in the long-term, epicardial pacing still seems to have a bigger number of complications(17,19) and so, it is advised that the initial choice between transvenous and epicardial pacing be made according to patient-specific factors(31): 1)patient size - some authors defend a limit weight at implantation of 5Kg(25) while others suggest a 10 Kg limit(5,32); 2) presence of cardiac and vascular malformations including a right-to-left intracardiac shunt – due to the 2 greater risk of thrombotic events(33)- and impossibility of venous access(11); 3) need for cardiac surgery(12); and 4) experience and expertise available in the unit treating these patients(5). It is also advised that a switch should be made to endocardial pacing in older children and adolescents(19,29).

PACING MODE: SINGLE- vs. DUAL-CHAMBER PACING

No studies directly compared single- with dual-chamber pacing however, it is suggested that both single- and dual-chamber modes are technically feasible and have a good short- and medium-term performance. Silvetti 2006(19) states that due to the large number of lead-related complications an effort should be made to reduce the number of implanted leads and later in a 2007 study, that VVI/R is the best choice outside the neonatal period(34). On the other hand, the same author in a more recent study mentions concerns regarding long-term

complications associated with VVI/R pacing mode(22). VDD appears as an alternative to single-chamber pacing mode while minimizing the number of implanted leads and although VDD is considered safe with a low complication rate(35), in the long-term it seems to be a temporary solution to bridge AV synchrony to DDD pacing(26). In what concerns dual-chamber pacing, Beaufort-Krol(6) suggests that children with congenital complete AVB (CCAVB) have LV dilation, that this dilation is progressive in those who required PM implantation but that it appears to regress in children with physiological (dual-chamber) pacing.

COMPLICATIONS ASSOCIATED WITH CARDIAC PACING

Children are a particular subset of patients with specific characteristics and consequently different pacing needs and complications than those of the adult population: 1) small body and vessel size which require leads and generators of smaller dimensions due to vascular concerns in transvenous pacing and surgical technique in epicardial pacing and which further the risk of in-operative complications; 2) predisposition to infections due to immune system immaturity in the youngest, some genetic anomalies frequently associated with CHD and frequent need of reoperation(36) and also because placement of a foreign-body by itself constitutes an infection risk; 3) higher resting heart rates with a bigger need for pacing activity and as such a shorter end-of-life battery capacity; 4) higher levels of physical activity with a bigger risk of lead damage and dislodgment as well as a greater need for PM rate adjustment when outstanding cardiac output is needed; 5) exponential somatic growth which may cause a transvenous lead to become under strain and consequently dislodge from its implantation site; and 6) most of these children will be pacing-dependent for the rest of their lives which translates to a need for PM system durability of up to 80 years same as a child's life expectancy while minimizing the number of associated complications.

To this extent, complications can be divided into 4 major clusters: procedure-related, implantation of a foreign-body related, lead-related and cardiac structure- and function-related. Procedure-related complications coincide with most early complications: hematoma, pneumothorax, hemothorax, pericardial effusion, cardiac perforation and, much rarer, phrenic nerve palsy. Those pertaining to the implantation of a foreign body comprise erosion, wound/pocket/lead infection, endocarditis, mediastinitis, venous occlusion, generator migration and abdominal hernia at pocket site. Lead related complications are by far the most frequent and include lead damage/fracture, intervention-related lead damage, insulation defects, increased excitability threshold, under/oversensing and loss of capture, exit block, early battery depletion, displacement, passage of a lead through a patent *foramen ovale*, lead strain, muscle stimulation and abdominal pain/irritability. Complications related to cardiac

structure and function mostly revolve around AV valve regurgitation (mainly tricuspid), AV desynchrony with associated pacing-induced ventricular dysfunction and rhythm anomalies.

Most of these complications are shared between both endocardial and epicardial pacing, yet there are some major differences. Endocardial pacing is most often associated with lead displacement especially in the early post-operative period, lead strain, venous occlusion, AV valve regurgitation or even rarer circumstances like the transvenous lead passing through a patent *foramen ovale*. Some of these can be curtailed by introducing new strategies: De Filippo 2018(23) suggests that using a Select Secure™ lead, together with the choice of axillary vein access, the creation of an intra-atrial loop of the leads and the placement of the generator in a sub-pectoral pocket, can reduce complication rate and ensure a safe and effective stimulation, up to 10 years of follow-up; Robledo-Nolasco 2009(32) suggests a subclavian venogram and progressive dilation of the subclavian vein for easier placement and lower the risk of vascular complications. In what concerns patient size and a higher risk of complications, most of the studies say that transvenous PM implantation in patients weighing 10 Kg or less is not only feasible but that it has good long-term outcomes with few complications. Konta 2016(25) describes their results with patients ≤10Kg saying that while there is an encouraging long-term outcome with documented venous patency at up to 25 years and original lead survival up to 17.6 years, a weight at time of PM implantation, inferior to 5 Kg appears to be a risk factor for subclavian vein occlusion whereas in those weighing 5 to 10Kg the risk was similar to older pediatric patients. Epicardial pacing seems to be most often associated with lead-related complications: lead damage, sensing anomalies, loss of capture, exit block, increased excitability thresholds, an earlier depletion of battery life and some rarer complications like phrenic nerve palsy, abdominal irritability/pain and mediastinitis. While recent studies have shown better results than previously because of the development of bipolar SE leads and beat-to-beat capture mode(10), these appear to be restricted to the short-term with transvenous SE leads still demonstrating fewer complications and better long-term outcomes(19,29).

Interestingly, in what concerns AV desynchrony, results obtained by Balaji 2017(37) seem to suggest that pacing-induced ventricular dysfunction occurred only in certain types of CHD. Also, Beaufort-Krol(6) suggest that dilated cardiomyopathy in CCAVB occurs early in the disease and does not develop during childhood, not even in children with LV dilation.

FREEDOM FROM LEAD FAILURE

When, in earlier studies, lead failure was extremely more common in epicardial leads, with the advent of SE leads, lead failure for epicardial PM systems has decreased with more

recent studies showing better results(15,16). Thomson 2004(15) refers to a survival of original lead at 75% at 5 years while on the other hand, Kubus 2012(10) expound on survival of original lead of 76% at 10 years. Furthermore, Thomson(15) also states that the only predictors for epicardial lead failure are SE lead technology and decade of implant which is in agreement with our observation. Remarkably, Konta 2016(25) presents a survival of original lead of up to 17.6 years with transvenous PM implantation.

SYMPTOM-FREE PATIENTS

Although only a small minority of the studies made direct reference to current patient symptoms, those that did(7,23,24) reported mostly, if not all, asymptomatic patients which goes to show the impact of PM therapy in the reduction of both mortality and morbidity when compared with natural history data(7).

ADVERSE EVENTS

There is no precise definition for adverse events, also adding to that fact, different studies don't always present the definition that was used to classify them as such which makes it difficult to assess the true incidence of these events as well as and any risk factors. Nevertheless, possible correlations have been mentioned with complex CHD(1) and with previous cardiac surgery(12).

PACEMAKER-RELATED MORTALITY

PM-related mortality was 0% in most studies and as high as 3.8% across the 6 studies(7–12) that mentioned PM-related deaths.

RECOVERY OF SINUS RHYTHM

A particular event that merits close attention during follow-up is the recovery of sinus rhythm which was mentioned to be as high as 8%(5). Although the recovery in these patients may seem reliable there is always a possibility of paroxysmal AVB, and so they should be followed up like all other PM patients(27). Still, the PM may be programmed to the lowest rate that would provide rate support in the event of complete heart block recurrence(27).

CONCLUSIONS

Initial choice between transvenous and epicardial pacing should be made according to patient size, presence of cardiac and vascular malformations, need for cardiac surgery and experience and expertise available in the unit treating these patients. Nevertheless, it should also be kept in mind that preservation of vascular access in younger patents ought to be privileged given that a pacing switch should be made from epicardial to endocardial pacing in older children and adolescents.

Most authors propose that dual-chamber pacing is the best alternative at long-term follow-up and that single-chamber pacing should act as a bridge to a later upgrade to physiological pacing.

Permanent cardiac pacing in pediatric patients appears to be an overall safe procedure with good short-, medium- and long-term results. However, there is a high rate of complications, mainly lead-related, especially in younger and smaller children(38). And so, it is suggested that PM implantation should be reserved for patients who weight more than 3 Kg and who are older 5 days of age(39). It is also recommended that a yearly echocardiographic and eco-doppler evaluation (regarding transvenous pacing) should be performed in all patients(6).

VII. LIMITATIONS

Major study limitations were the diminished number of studies, the age of some of those studies -which not only do not comply with recent guidelines on the appropriate structure for said studies, but which also do not reflect the current advances in generator and lead technology -, small sample sizes -the biggest study had 292 patients while one study had no more than 7 patients-, and finally the age disparity between pediatric patients since, as concluded, different age groups have different characteristics and pacing needs.

VIII. FUNDING AND CONFLICTS OF INTEREST

None declared.

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