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Chronic ventricular pacing in children: toward prevention of pacing-induced heart disease

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Abstract In children with congenital or acquired complete atrioventricular (AV) block, ventricular pacing is indicated to increase heart rate. Ventricular pacing is highly beneficial in these patients, but an important side effect is that it induces abnormal electrical activation patterns. Traditionally, ventricular pacemaker leads are positioned at the right ventricle (RV). The dyssynchronous pattern of ventricular activation due to RV pacing is associated with an acute and chronic impairment of left ventricular (LV) function, structural remodeling of the LV, and increased risk of heart failure. Since the degree of pacing-induced dyssynchrony varies between the different pacing sites, 'optimal-site pacing' should aim at the prevention of mechanical dyssynchrony. Especially in children, generally paced from a very early age and having a perspective of life-long pacing, the preservation of cardiac function during chronic ventricular pacing should take high priority. In the perspective of the (patho)physiology of ventricular pacing and the importance of the sequence of activation, this paper provides an overview of the current knowledge regarding possible alternative sites for chronic ventricular pacing. Furthermore, clinical implications and practical concerns of the various pacing sites are discussed. The review concludes with recommendations for optimal-site pacing in children.

Keywords Pacing · Pediatrics · Dyssynchrony · Ventricular · Prevention

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Introduction

While the majority of patients receiving pacemakers are adults at usually advanced age, a small group of pacemaker recipients are children, even newborns. Results and conclusions from pacing studies in adults are not readily transferable to the pediatric population, because diseases and causes of dyssynchrony and heart failure differ strongly. In adults, indication for pacemaker therapy or cardiac resynchronization therapy (CRT) concerns, among others, bradycardia, left ventricular (LV) dysfunction, and dyssynchrony due to partially diseased conduction systems often combined with degenerative diseases and infarctions of the myocardium. In children, it typically concerns bradycardia due to complete atrioventricular (AV) conduction block, usually associated with healthy myocardium. Albeit AV block may exist "isolated" in structurally normal hearts, in children and young adults AV block is often combined with abnormalities in cardiac anatomy. In structurally normal hearts, AV block may either be congenitally induced by maternal autoantibodies (e.g., anti-SSA (Ro), anti-SSB (La)) or be acquired by infectious diseases or progressive AV-conduction tissue fibrosis. In children with structural congenital heart disease, AV block

may either be associated with the structural disease itself or be induced by surgical or percutaneous procedures performed.

In patients with complete AV block and bradycardia, ventricular pacing is indicated to increase heart rate, rather than to 'resynchronize' electrical activation. In addition to the obvious beneficial effects of the restoration of heart rate, the unpredictable risk of sudden cardiac death as well as LV failure associated with untreated complete heart block is cured by chronic ventricular pacing [1, 2]. Therefore, AV block associated with symptomatic bradycardia is a class I indication for ventricular pacing therapy [3]. Despite the fact that ventricular pacing is highly beneficial in patients with completely blocked intrinsic conduction, it does not resemble nature. In contrast, ventricular pacing induces an abnormal electrical activation pattern, which may cause mechanical dyssynchrony, associated with impairment of pump function, LV remodeling, and increased risk of heart failure [4–10]. Right ventricular (RV) pacing, rather than etiology of AV block, has even been identified as an independent risk factor for the development of LV dilatation and dysfunction following chronic pacing [11, 12]. In deduction, in patients with complete heart block requiring chronic ventricular pacing, the prevention of mechanical dyssynchrony and thus the prevention of functional as well as structural deterioration seem a major challenge in addition to the restoration of heart rate. Especially in children, generally paced from a very early age and typically having normal myocardial function at the initiation of pacing, as well as having a perspective of life-long pacing, the preservation of cardiac function during chronic ventricular pacing should take high priority.

The objectives of this paper are (1) to elucidate the importance of the sequence of activation in the pathophysiology of ventricular pacing, (2) to review several sites for chronic ventricular pacing, (3) to discuss clinical implications of the various sites for ventricular pacing in children, and (4) to give recommendations for optimal-site pacing in children.

(Patho)physiological background of ventricular pacing

Normal electrical activation

Under physiological circumstances, the electrical impulse given by the sinus node is transmitted to the AV node and is then rapidly conducted, via the specialized His-Purkinje conduction system, to both ventricles simultaneously resulting in 'synchronous' electrical activation of the heart. Literally, "synchronous activation" denominates simultaneous activation of all ventricular myocytes, which is not achieved under physiological circumstances. Despite the rapid propagation (3–4 m/s) of the electrical impulse through the conduction tissue, activation of the ventricles occurs over a certain amount of time. Normally, electrical activation starts at the endocardium of the apex and progresses toward the epicardium, as well as upwards to the base, resulting in a coordinated and energetically efficient mechanical contraction, which is crucial for optimal LV performance. Therefore, the term "euchrony" would more correctly describe the normal timing and sequence of ventricular activation under physiological conditions. However, "electrical synchrony" and "synchronous activation" are generally used in the literature to denominate the physiological timing and sequence of electrical activation and are accordingly used throughout this paper. During normal activation, synchrony is observed between the ventricles (interventricular synchrony) and within each ventricle (intraventricular synchrony). LV-intraventricular electrical synchrony during normal activation is illustrated by the left upper panel of Fig. 1.

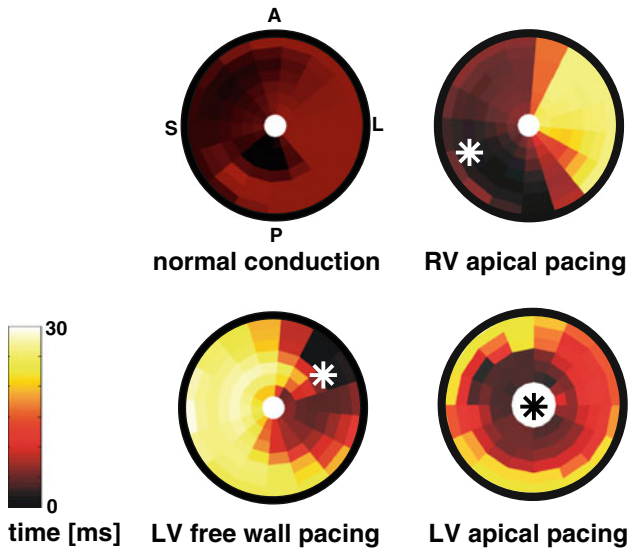

Fig. 1 Left ventricular endocardial activation in canine hearts. Electrical activation mapping using a left ventricular (LV) intraventricular mapping catheter in canine experiments (described by Verbeek et al. JACC 2003), during normal activation, pacing from the right ventricular (RV) apex, LV free wall, and LV apex, respectively. The electrical activation maps are presented as bull's eye plots with the inner disk representing the LV apex and the outer disk representing the LV base. The letters A, P, S, and L indicate the anterior, posterior, septal, and lateral wall, respectively. Electrical activation of the LV is fast and synchronous during normal activation. During ventricular pacing, the region in the proximity of the pacing site is early-activated, whereas myocardium remote from the pacing site is late-activated. In LV apical pacing, electrical activation is circumferentially synchronous. * = ventricular pacing site

Pathophysiology of ventricular pacing

During ventricular pacing, the initiation and the sequence of electrical ventricular activation are different from those in normal physiological circumstances. From the site of pacing, the electrical activation wave spreads over the ventricles through the slowly transmitting myocardium, instead of through the rapidly conducting specialized conduction system. Slow cell-to-cell transmission of the electrical impulse results in asynchrony of electrical ventricular activation, with early activation of the myocytes close to the pacing site and delayed activation of the cells in remote regions (Fig. 1). Consequently, early systolic shortening of the early-activated myocytes results in stretch of late-activated myocytes, rather than that it results in the onset of the ejection phase. When myocytes in remote regions are subsequently activated and start to contract, they contract even more powerfully due to the early systolic pre-stretching (known as the local Frank–Starling mechanism) [4]. Hence, electrical asynchrony, as induced by ventricular pacing, results in a dyssynchronous contraction pattern. The mechanical dyssynchronous contraction pattern is associated with a reduction in LV pump function by an asymmetric redistribution of mechanical workload in the myocardium, which in turn results in a redistribution of oxygen demand and perfusion, as well as in asymmetrical hypertrophy [13–16].

Since the degree of pacing-induced dyssynchrony varies between the different pacing sites (Fig. 1), the site for chronic ventricular pacing should be carefully selected, so that adverse mechanical dyssynchronization is minimized. In order to propose which site(s) may be optimal for chronic ventricular pacing in children, it is necessary to critically appraise the various pacing sites in the context of mechanical activation patterns and cardiac function.

Ventricular pacing sites

Conventional pacing sites: right ventricular apex and free wall

Traditionally, ventricular pacemaker leads are positioned at the RV. The RV apex and free wall are easily accessible, either at the epicardium via a surgical implantation or at the endocardium by means of a transvenous approach. These RV pacing sites are readily identified and associated with stable lead position and reliable chronic pacing parameters (e.g., capture). However, chronic RV pacing is associated with deleterious effects in functional and structural outcome [5–10]. In hearts with normal left–right anatomy, during RV pacing, a left bundle branch block (LBBB) pattern of activation is created [4, 7, 17, 18]. This pattern is characterized by early activation of the RV and septum and delayed activation of the LV lateral wall, implicating electrical and mechanical asynchrony between the ventricles (interventricular asynchrony), as well as within each ventricle (intraventricular asynchrony). Since the RV free wall starts to contract before the interventricular septum and the LV free wall, RV pressure increases before LV pressure is built up. As a consequence of this abnormal early systolic pressure gradient over the interventricular septum, the septum bulges into the LV, which can be observed as paradoxical movement of the septum [19].

Although the dyssynchronous pattern of ventricular activation due to RV pacing is well tolerated in most children [20, 21], several studies have shown that this pattern is associated with an acute and chronic impairment of LV function, structural remodeling of the LV, and increased risk of heart failure [5, 6, 22]. Though overt heart failure is reported in about 7% and impaired LV function in up to 13% of the chronically RV-paced pediatric patients after follow-up for about one decade [5, 10, 12, 20], the actual incidence of ventricular dysfunction in relation to chronic RV pacing remains undefined and may be even higher for life-long follow-up.

The recognition of the potentially deleterious effects of RV pacing has initiated the search for alternative sites for chronic ventricular pacing. In addition to the traditional RV apex and free wall sites, several other sites within the RV became accessible by advances in pacemaker-lead technology and implant approaches and began to be clinically explored. Also, biventricular pacing has been introduced in children, which can be achieved by the insertion of an additional lead at the LV epicardium (either transvenously throughout the coronary sinus or surgically). Usually, surgical approaches are preferred for all lead implantation in small children or children undergoing cardiac surgery, implicating that there is to a great extent freedom to position the lead at the epicardium of either the RV, or the LV, or even at both.

Alternative-site RV pacing

Both terms '*alternative-site RV pacing*' and '*selective-site RV pacing*' refer to pacing at sites other than the RV apex or free wall, though either located within or approached via the RV. These sites are selected based on the (individual) prospect of a more physiological electrical activation pattern and a better hemodynamic response with less detrimental remodeling.

By lead insertion through the RV, the His bundle may be paced directly in order to restore the normal pathway of electrical conduction system. In patients without distal conduction abnormalities, *His-bundle pacing* would obviously induce a normal physiological sequence of activation

and therefore prevent the heart from dyssynchronous activation and the harmful effects associated. Indeed, beneficial effects of successful His-bundle pacing have been reported in adults with AV-nodal ablation for atrial fibrillation [23, 24]. Although technical advances have improved the success rate of His-bundle pacing [25], implantation in this very small region is a challenging procedure and seems not very applicable in children. Moreover, especially in children with surgically induced AV block, but also in children with congenital AV block, the His bundle may be involved in the pathological interruption of the conduction system, implicating that there is no rationale left for direct His-bundle pacing.

Within the field of research on alternative RV pacing sites, also the *RV outflow tract* has been extensively investigated. Unfortunately, the term RV outflow tract pacing is not always clearly defined in literature and has been used to describe a variety of RV pacing sites, including the true outflow tract and mid-septum. Nonetheless, the differentiation between the diverse sites within the conical RV outflow tract is very important, as activation patterns and wave propagation will differ depending on the exact anatomical position of the lead [26, 27]. Not surprisingly, studies with regard to the effects of RV outflow tract pacing without specification of exact anatomical definition of the site have shown inconsistent results [28, 29]. Most consistently, beneficial effects for RV outflow tract pacing have been found in studies clearly mentioning to pace from the septal side of the RV outflow tract (also defined as "high septal" or "para-Hisian" pacing) [22, 30–35]. Thus, in RV outflow tract pacing in particular, the septal side of the outflow tract may be a target. Nevertheless, it should be noted that 'septal RV outflow tract' is not a good definition, since the upper part of the 'septal side' within the RV outflow tract is located above the LV. Therefore, only *the inferior part of the septal side of the RV outflow tract* can be considered as truly septal and may be the preferred location for lead placement in the RV outflow tract [26, 27].

Biventricular pacing

The concept of biventricular pacing is to synchronize electrical and mechanical activation by electrical stimulation of both ventricles. Biventricular pacing is mainly applied in adult heart failure patients with normal cardiac anatomy, suffering from LV dysfunction in association with LV dyssynchrony due to intrinsic LBBB. Since in these patients, biventricular pacing is applied in order to resynchronize electrical activation, it is often defined as "cardiac resynchronization therapy" (CRT).

Numerous studies have indicated that in the majority of the adult patients with heart failure and conduction system disease, biventricular pacing improves LV function and reverses LV remodeling as well as that it reduces clinical symptoms and decreases mortality [36–38]. Based on the rationale that the sequence of activation in RV pacing is similar to the activation pattern in LBBB, application of biventricular pacing has been extended to heart failure patients with RV-pacing-associated dyssynchrony. Indeed, also in patients with a history of chronic RV pacing and mild to severe cardiomyopathy, biventricular pacing is beneficial concerning LV geometry and function, as well as regarding clinical symptoms [39–42].

The data from large randomized adult CRT trials cannot simply be translated to children with cardiac failure, because the pediatric population not only includes children with normal cardiac anatomy and LV failure but also includes children with univentricular hearts (with either RV or LV morphology), hearts with a systemic RV (i.e., heart with either congenitally corrected transposition of the great arteries or transposition of the great arteries with atrial switch procedure in the past), and hearts with RV failure (e.g., RV failure associated with corrected tetralogy of Fallot). In addition, a substantial number of pediatric CRT candidates have ventricular dyssynchrony and cardiac failure related to conventional pacemaker therapy for postoperative or congenital AV block. Nonetheless, encouraged by the positive results in adults, biventricular pacing meanwhile has also been applied in children with ventricular dysfunction. In these children, with either isolated AV block or AV block combined with structural heart disease, biventricular pacing (often following chronic RV pacing) improved pump function and reversed ventricular remodeling. Upgrade from single-site RV pacing to biventricular pacing was at least as effective as in upgrade to biventricular pacing in adults with heart failure, and in some children, the need for cardiac transplantation was even deferred [43, 44]. From the analysis of Janousek et al., the response to biventricular pacing seems to be dependent on the structural and pathophysiological substrate, being most favorable after upgrades from single-site RV pacing to biventricular pacing in patients in whom the LV is the systemic ventricle [44]. Noteworthy, in these studies, resynchronization was mostly indicated for decreased LV function following chronic conventional RV pacing [44, 45]. Although biventricular pacing is better in comparison with RV pacing, it may not be as good as normal intrinsic activation in healthy hearts [46, 47].

Single-site left ventricular pacing

Comparable to that of upgrade to biventricular pacing, in children with LV dysfunction after chronic RV pacing, functional improvement and reverse remodeling are reported for *LV single-site pacing* [48, 49]. Although

important, this finding was not very surprisingly as LV pacing had already been shown to acutely increase pump function when compared with RV pacing in laboratory dogs and in children undergoing cardiac surgery [17]. In dogs with experimental complete AV block, Mills and colleagues showed that LV apical and LV septal pacing resulted in only moderate electric desynchronization as well as in minor redistribution of mechanical work and perfusion [50]. Even after 4 months of pacing in these dogs, LV pacing induced normal levels of contractility, relaxation, and myocardial efficiency. Moreover, single-site LV apical and LV septal pacing maintained normal cardiac function and efficiency, at least as well as biventricular pacing [50]. In line with these findings, in adult heart failure patients, single-site LV pacing resulted in the same improvement in LV function as during acute or chronic biventricular pacing [51–53]. It is argued that single-site LV pacing in LBBB patients results in "hidden resynchronization" by fusion of the activation front originating from the left lateral pacing electrode with the impulse traveling through the right bundle. However, benefits of single-site LV pacing are observed during pacing with short AV delays [53] and in patients with atrial fibrillation [52], making the hypothesis of "hidden resynchronization" very unlikely to be applied for all patients.

We postulate that, above and beyond synchrony, the sequence of activation is a major determinant of cardiac pump function [4, 54]. During LV (free wall) pacing, the prolonged duration of total activation is comparable with the delay during RV pacing, which is reflected by a similar prolongation of the QRS duration [55]. However, during LV pacing, the LV lateral wall is activated prior to the septum and RV lateral wall, preventing the septum from paradoxical movements and resulting in superior hemodynamic performance when compared to RV pacing [19]. On top of that, a physiological apex-to-base sequence of activation is induced by LV apical pacing, which results in synchronous electrical activation and contraction at the circumferential level of the LV (Fig. 1) [46, 47]. This hypothesis is supported by the observation of Gebauer et al. that LV apical pacing, compared with other sites, preserves septal to lateral LV synchrony and systolic function [56], as well as by other studies showing that LV apical pacing maintains cardiac function at a normal level [17, 50].

In some centers, based on surgical preferences, chronic single-site LV pacing has been applied in children for already several years [57]. Small studies in children of one of these centers show that chronic LV free wall pacing may preserve LV function and LV dimension at a level of healthy controls [49, 55, 58]. Currently, a multicenter study is carried out to retrospectively and cross-sectionally evaluate long-term influences of various pacing sites on LV function and dyssynchrony in structurally normal hearts. Preliminary results from this study indicate that single-site LV pacing results in better LV function and mechanical synchrony when compared to RV pacing [59, 60].

Clinical implications and practical considerations

In children, resynchronization of dyssynchrony induced by RV pacing, or, preferably, prevention of mechanical dyssynchrony (in case of 'de novo pacing'), must take high priority. Biventricular pacing, as well as single-site LV apical and LV free wall pacing seem all promising in the young, concerning preservation and restoration of pump function. This raises the question whether or not such pacing therapies should be applied in all children with an indication for chronic ventricular pacing.

Individual approach for optimal pacing sites

Although complete AV block is often combined with structural heart defects, only children with an isolated heart block were included in most studies concerning the effects of various pacing sites. The ever-improving survival after surgery for complex congenital heart disease broadens the variety of anatomical substrates and indications for chronic ventricular pacing. Thus, the pediatric pacing population is highly heterogeneous in terms of age and cardiac anatomy. This implicates that findings from studies in adults or children with structurally normal hearts cannot easily be extrapolated to the entire pediatric pacing population. Therefore, an individual approach may be the best way to identify the "optimal pacing site".

It seems reasonable to assume that in patients with abnormal anatomy or cardiac function, the optimal sequence of activation may be different from the optimal sequence of activation in anatomically normal hearts. Indeed, in patients with RBBB and RV failure after surgically repaired tetralogy of Fallot, RV pacing has been proposed as a potential therapy for RV failure [61–63]. Nevertheless, other studies on effects of pacing sites in these patients suggested that, when both RV and LV function are concerned, biventricular pacing may be superior to RV pacing [64, 65]. Further investigations are required to confirm these findings and to determine whether pacing the late-activated ventricle (i.e., RV) or biventricular pacing in these patients is worthwhile [66].

Although upgrade to biventricular pacing seemed to be most favorable in patients in whom the LV is the systemic ventricle [44], the beneficial effects of biventricular and single-site LV pacing have been observed in a mixed pediatric population [12, 43–45].

Especially in children with abnormal cardiac anatomy, influences of different pacing sites on cardiac function are

not well known. To find the optimal pacing site in children with abnormal anatomy, various pacing sites should be individually investigated for their effects on electrical activation and cardiac function. Given the absence of a consistent correlation between cardiac function and paced QRS duration in acute and chronic pacing studies, we discourage the use of QRS duration as a tool for the selection of an optimal epicardial pacing site in children [17, 55, 67, 68]. A better approach in this respect may be the use of ECG imaging, which noninvasively images electrical activation patterns [69, 70], although the optimal activation pattern for the diverse anatomical substrates is not known yet. Therefore, and since the intention of optimal-site pacing is to preserve cardiac function, it may be even better to measure pump function by either (non-invasive) hemodynamic or echocardiographic parameters while pacing from various pacing sites, and implant the lead at the site where pacing results in the best pump function.

Practical considerations

In addition to functional rationales behind ventricular lead positions, practical aspects should be taken into account when choosing the optimal site of pacing for rate control in the individual patient. First of all, in children with (complex) congenital heart defects, restrictions in lead placement could be introduced by anatomy, prior surgery or scarred myocardium. Secondly, a major practical advantage of single-site pacing, compared with biventricular pacing, is that only one ventricular lead is needed, prolonging battery longevity and reducing potential vascular problems and lead-associated complications. Because every (re)placement of either a lead or generator comes with risks of complications, the number of replacements should be minimized, especially in children, since they have a perspective of life-long follow-up. Thus, single-lead pacing should be seriously considered.

With respect to the technique of lead positioning, in older children and adult patients, leads are often transvenously inserted and endocardially positioned at the RV apex or septum, because it is technically safe, fast, and reliable. In neonates and small children, most centers preferably use epicardial lead placement by a surgical approach. Epicardial lead placement is also preferred in children with an open connection to the systemic ventricle, because the presence of endocardial leads increases the risk of embolism. Since possibly successful alternative RV pacing sites require a transvenous approach for lead implantation, these sites are probably not feasible in small children. For the purpose of single-site LV pacing, the epicardial LV apex or, alternatively, the LV free wall can easily be approached through a (limited) sternotomy, sub-xiphoidal incision or left lateral thoracotomy [57], with good lead stability and pacing performance, as well as excellent cosmetic results. In larger children and adults, in whom a transvenous approach may be preferred, single-site LV pacing might also be achieved by implantation via the coronary sinus, though for single-site LV pacing, it is recommended to position the ventricular lead as far to the apex as possible [17, 55]. Future perspectives for lead insertion for LV pacing are a trans-septal approach to endocardial LV septal pacing sites [50] and "wireless" pacing [71, 72]. As soon as both are clinically applicable, pacing could be achieved from any of the diverse endocardial sites in the systemic ventricle.

Recommendations for optimal pacing in children

Based on the (patho)physiological background of ventricular pacing and the current knowledge regarding the various pacing sites, as well as on clinical and practical aspects, we would like to give recommendations for optimal pacing in children. Our recommendations and suggestions for pacing in children with normal cardiac anatomy and structural heart defects are schematically displayed in Fig. 2a and b, respectively.

First of all, because by definition, ventricular pacing alters the physiological pattern of electrical activation, ventricular pacing should be avoided (or minimized) in patients with (partially) preserved AV conduction and intact His-Purkinje system, such as sick sinus syndrome [73, 74]. Also, in children with chronic ventricular pacing for surgically induced AV block, the existence of underlying ventricular rhythm by re-established AV conduction should be regularly checked, as very late recovery of AV conduction is reported to occur [75].

In children with AV block and structurally normal hearts, we advocate the use of single LV apex and LV free wall sites as the preferred sites for ('de novo') chronic ventricular pacing [55, 58–60, 76]. It is recommended to preferably avoid pacing from the RV free wall [12]. However, in young adults receiving a first pacing system or having a system replacement, the routine transvenous approach seems justifiable in the context of practical aspects, since RV apical pacing is well tolerated by most patients [20, 21] and since change to single-site LV pacing, as well as upgrade to biventricular pacing, induces reversal of remodeling and reversal of the impaired LV function in deteriorated hearts after pacing [41, 43, 44, 48, 49].

Regular echocardiographic checkup is warranted in all pediatric patients with pacemaker therapy, and especially in children who are paced at the RV. Changing the site of pacing to either biventricular or single-site pacing at the

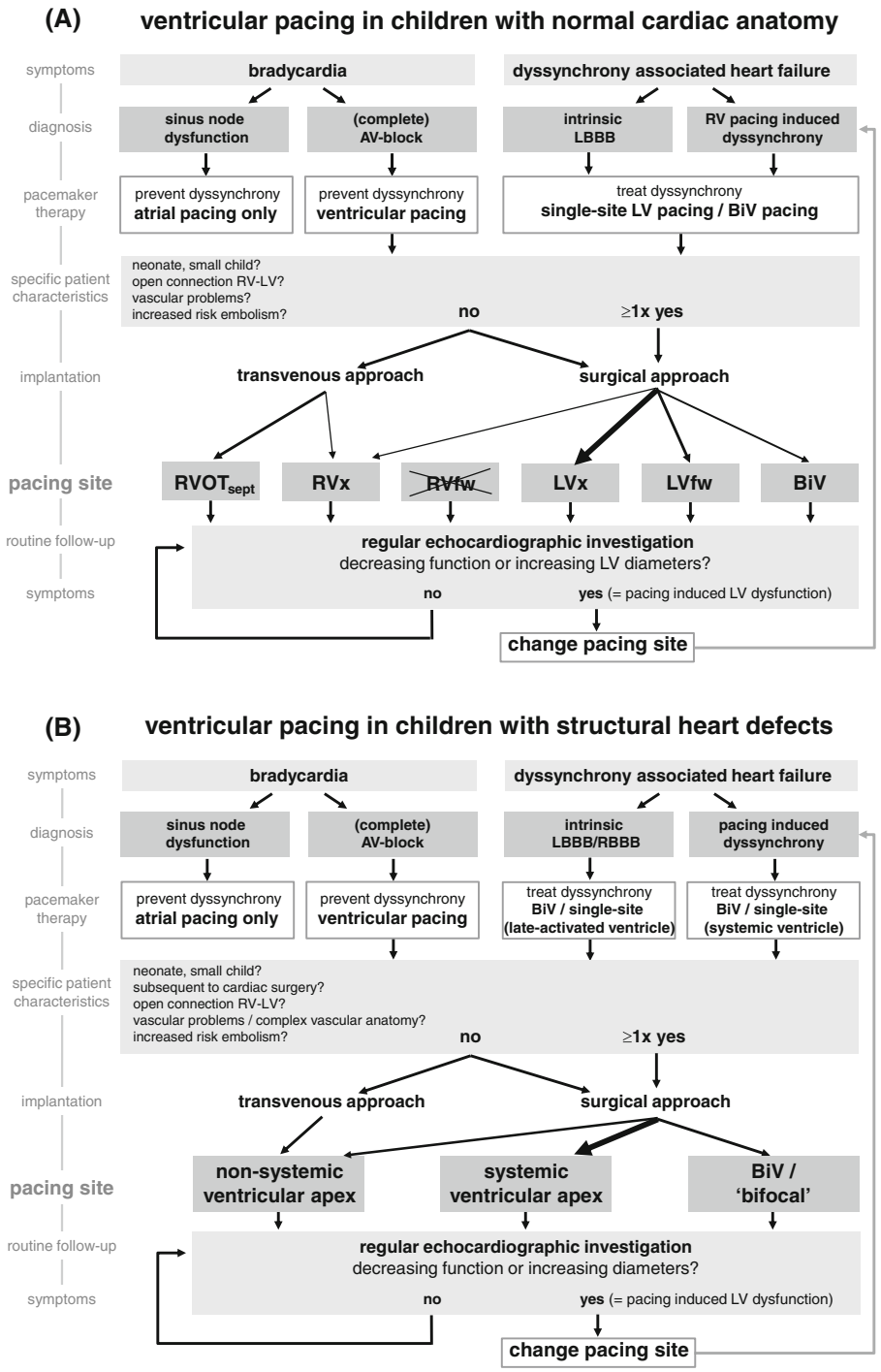

Fig. 2 Recommendations for optimal pacing in children; a schematic overview. An individual approach may be the best way to identify the "optimal pacing site". In order to choose the optimal pacemaker therapy for the individual patient, one should discriminate between pacing approaches aiming at the prevention of dyssynchrony and the ones that resynchronize (treat dyssynchrony). In children with AV block and normal cardiac anatomy, (**a**) we advocate the use of single LV apex and LV free wall sites as the preferred sites for chronic ventricular pacing. In young adults, the routine transvenous approach to the RV apex seems justifiable in the context of practical aspects. It is recommended to avoid pacing from the RV free wall, both endocardially and epicardially. In children with structural heart defects, (**b**) we suggest to implant the lead for chronic ventricular pacing preferably at the systemic ventricle if a surgical approach is also practically advised. Regular echocardiographic checkup is warranted in all pediatric patients with pacemaker therapy. Changing the site of pacing to either biventricular or single-site pacing should be considered as soon as echocardiography reveals signs of ventricular dilatation or dysfunction. *AV block* atrioventricular block, *LV* left ventricle/ventricular, *RV* right ventricle/ventricular, *LBBB* left bundle branch block, *RBBB* right bundle branch block, $RVOT_{sept}$ the inferior part of the septal side of the RV outflow tract, *RVfw* RV free wall, *RVx* RV apex, *LVx* LV apex, *LVfw* LV free wall, *BiV* biventricular RVx (or RVfw) + LVfw. *leads should be placed preferably at the ventricular apex

systemic ventricle should be considered as soon as echocardiography reveals signs of ventricular dilatation or dysfunction.

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