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Cardiac pacing in pediatrics: Is still the right ventricle the optimal pacing site?

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Acronyms
CAVB: complete atrioventricular block
HF: heart failure
LV: left ventricle
LVA: LV apex
LVEF: left ventricular ejection fraction
pQRS: paced QRS
RV: right ventricle
RVA: right ventricular apex
RVOT: outflow tracts of the RV

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ABSTRACT
Permanent cardiac pacing is frequently indicated in pediatric patients due to atrioventricular block. Traditionally, the right ventricle has been the pacing site because it is readily accessible, and provides lead stability and optimal chronic pacing thresholds. However, it is associated with a dyssynchrony pattern of ventricular activation, that may cause remodeling and impairment of left ventricular function. In pediatric patients, paced from an early age and with a long life expectancy, the preservation of cardiac function is a premise. Therefore, the prevention of dyssynchrony, using possible alternative sites, is not just a priority, is a challenge. The aim of the article is to show the effects of chronic right ventricular pacing as well as the evidence of benefits provided by alternatives pacing sites in pediatric population and their clinical and practical implications.
Key words: Ventricular pacing, Pediatrics, Dyssynchrony, Ventricular function

Estimulación cardíaca en pediatría: ¿sigue siendo el ventrículo derecho el sitio óptimo?

RESUMEN
La estimulación cardíaca permanente se indica en pediatría, con mayor frecuencia, debido al bloqueo aurículo-ventricular. El ventrículo derecho ha sido tradicionalmente el sitio estimulado, dada la factibilidad del acceso, la estabilidad del electrodo y el mantenimiento de umbrales crónicos adecuados. Sin embargo, dicha estimulación se asocia a un patrón disincrónico de activación ventricular, que puede producir remodelado y deterioro de la función ventricular izquierda. En la población pediátrica, donde la estimulación se inicia muchas veces desde edades tempranas y con una larga expectativa de vida, constituye una premisa la preservación de la función cardíaca, por lo que la prevención de la disincronía mediante la utilización de sitios alternativos de estimulación, más que una prioridad, constituye un reto. El presente artículo tiene el objetivo de mostrar los efectos de la estimulación ventricular derecha, así como las evidencias demostradas del beneficio e implicaciones clínicas y prácticas de los sitios alternativos de estimulación en la población pediátrica.
Palabras clave: Estimulación ventricular, Pediatría, Disincronía, Función ventricular

INTRODUCTION

The most common indication for electrical pacing of the heart in pediatrics is the complete atrioventricular block (CAVB), congenital or acquired. As in adult population, the right ventricle (RV) has traditionally been the pacing site for being more accessible, stability of the long-term electrode catheter as well as keeping adequate chronic thresholds. Depending on the patient's age and preferences of each institution, the pacemaker is implanted via epicardium preferably in the RV free wall, or via endocavitary in the right ventricular apex (RVA). However, pacing from these sites induces a dyssynchronous contraction pattern characterized by an early activation of the RV and the interventricular *septum*, and a delayed activation of the lateral wall of the left ventricle (LV)[1].

This pattern produces an electrical and mechanical interventricular asynchrony as well as intraventricular asynchrony[1]. Although this deleterious effect is tolerated in most cases[2,3],many investigations[4-7] demonstrate that chronic pacing from the RV is a major risk factor for acute or chronic deterioration of the left ventricular function, structural remodeling of the LV and increased risk of heart failure (HF), which has been reported between 6-13% of pediatric patients followed up for a decade[4,7-10].

Right ventricular pacing effects

Under physiological conditions, the electrical activation of the ventricular myocytes starts from the endocardial apex region and progresses toward the basal epicardial regions (**Figure 1A**), which produces a coordinated mechanical contraction, energetically efficient that ensures an optimal left ventricular function. During this normal ventricular activation sequence takes place a synchrony between the two ventricular chambers (interventricular synchrony), and between different segments of each of the ventricles (intraventricular synchrony).

Meanwhile, artificial pacing from the free wall and RAV (**Figure 1B**) produces changes in the start, sequence of electrical activation and contractile pattern. A wave of depolarization extends from the paced site and undergoes a slowing on the myocyte-myocyte conduction in its expansion to the rest of the myocardium, which causes an asynchronous pattern of left bundle branch block, characterized by an early activation of myofibrils nearby the site of pacing (RV and *septum*), with a delayed depolarization of the most distant regions (lateral wall of the LV)[11-13]. This asynchrony causes the regions near the paced site to "pull" those that have not been activated yet, delaying the shortening and increasing the local contraction strength by the Frank-Starling mechanism. Likewise, the late-depolarized regions entail a burden to the early-activating regions. The outcome is a less effective and energetically less productive contraction, because the contraction of the early-depolarized regions occurs when the LV pressures are still low and the ejection phase has not started, to which is added the consumption of energy generated in the afore said region due to the "stretching" effect on the late activated myofibrils[11]. Dyssynchronous contraction, with consequent asymmetric redistribution of the intraventricular mechanical load, also leads to a regional reduction of the perfusion and myocardial oxygen consumption[13].

The pattern of asynchronous activation not only involves the ventricular hemodynamics but also contractility, relaxation and hence cardiac output (**Figure 2**). The pump function damage is expressed by a de-

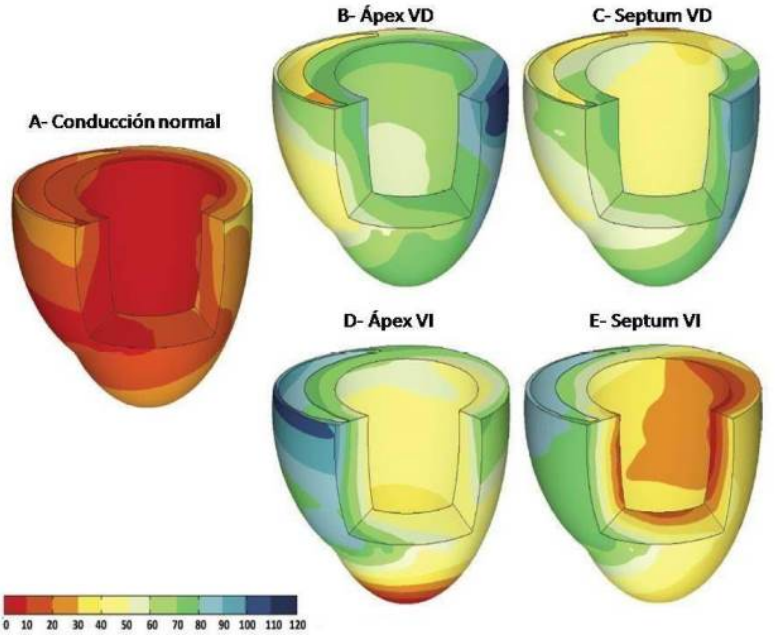

Figure 1. Map of electrical activation during: **A.** Normal driving **B.** RVA, **C.** RV septal region, **D.** LVA, **E.** LV septal region. The color bar shows the activation time in milliseconds. Adapted from Mills *et al.* Cir Arrhythmia Electrophysiol. 2009; 2: 571-9[33], with permission.

creasing of hemodynamic variables such as systolic volume and work and a slow increase in left ventricular pressures, plus the deviation to the right of the tele-systolic/volum pressure curve[12]. Also, the loss of ventricular interdependence is crucial in the origin of the paradoxical movement of the partition accompanying RV pacing. At first, when you start the contraction of the RV free wall, it establishes a systolic pressure gradient on the *septum*, with the consequent loss of septal contribution to the left ventricular ejection. Moreover, the pattern of abnormal relaxation finds expression in the decreasing slope dp/dt, E wave velocity and the diastolic filling time; these changes lead to prolonged times of isovolumetric contraction and relaxation, which leads to a preload reduction[11-13.]

There are different deleterious structural effects that have been described long term[14-16]. Pathological findings, observed in endomyocardial biopsies of the RV mid-septal regions[14] show variations in the myofibrils size, presence of fatty deposits, prominent Purkinje cells, mitochondrial morphological changes and areas of calcification, fibrosis, dystrophies and sclerosis. Chronic disorders also include changes in autonomic tone, anatomical remodeling of the ventricles (dilation and asymmetric hypertrophy)[16] and changes in ion channels, one of whose expressions is the change in the ventricular repolarization front, which may persist even when pacing has ceased (electrotonic memory)[17].

There is enough research on adult population[11,16,18,19] showing how electromechanical dyssynchrony leads to remodeling and asymptomatic dysfunction of the LV in 50% of patients, with clinical expression of left ventricular failure in 10% of cases . There are several factors identified as triggers of LV failure in this population, among them: dyssynchrony, adverse remodeling, left atrioventricular dyssynchrony and the development of dysfunctional mitral regurgitation[12].

Asynchrony as a primary factor consists of three main elements: the dose of asynchrony, time, and the substrate related to it. As an evaluative measure of the ventricular dyssynchrony burden we have taken the pacing percentage and width of the paced QRS (pQRS), hence there is a high HF risk related to a greater pQRS percentage and width[11,20,21]; Likewise the risk is increased in subjects with preexisting intraventricular conduction disturbances and left ventricular ejection fraction (LVEF) decreased or bordering[22-24]. However, the results and conclusions of these estudies[20-24] in the adult population cannot be extrapolated to the pediatric population because of the difference in terms of morbidity, dyssynchrony causes and HF; in fact, results[5,7-10,25-27] in this age group are controversial. On the one hand, Chiesa *et al*.[10] reported an incidence of 8% HF in children paced from the RVA, manifested at an average primo-implant age of only 3 years; These authors[10] concluded that a percentage of 100% of ventricular pacing and the presence of wide pQRS are risk predictors. Moreover, Kim *et al.*[8] found deterioration in functional class by 6% of patients, but obvious 15 years later of the initial pacemaker implantation, which suggests that pediatric patients tolerate chronic pacing from the RV despite the above-cited adverse effects. Our group[27] considers the pQRS width is not a reliable parameter of mechanical dyssynchrony in pediatric patients, since this only reflects the total electrical activation time but not the activation sequence, so the ventricular activation sequence must be considered over pQRS duration, percentage, or pacing time.

There are several investigations[7,25-27] showing no correlation between the deterioration of the pumping function and the pacing time, pacing mode, associated congenital heart disease, CAVB etiologic diagnosis and pQRS width. Gebauer*et et al*.[7] designed a retrospective study to identify risk factors related to remodeling and left ventricular dysfunction in patients with CAVB pacemaker and with 100% ventricular pacing. They[7] found the highest incidence of damage to the LV ever published (13.6%), which was more common in individuals with CAVB of surgical cause which, without a significant statistical correlation, may suggest that the CAVB in the field of a congenital heart disease has an increased risk of developing ventricular dysfunction. Finally, they identified pacing from the RV free wall as the only significant predictor of risk of remodeling and involved left ventricular function [OR = 14.3; confidence interval 95% (2.3-78.2), p <0.001], whereas found no difference in pQRS width in patients with preserved LV function and those with cardiac failure[7].

Recently, in a multicenter study, Janousek *et al*.[26] evaluated 171 patients with pacing from different parts of the LV and RV, and detected a significant worsening of the shortening fraction and left ventricular ejection in subjects paced from the RV, hence, pacing from both freewall and sidewall of the RV is an independent predictor of significant deterioration (LVEF≤ 45%); this decrease was correlated with the degree of

dyssynchrony. In addition, our group[27] managed to assess sistole-diastolic function and synchrony in 80 patients with pacing from the LV apex (LVA) and RVA, with ≥ 95% pacing. There were important differences between the two groups in terms of systolic function parameters and intra-and interventricular synchrony, which were involved in patients with pacing from the RVA, with an incidence of 6.3% clinical dysfunction. The study[27] identified as risk predictors, pacing from the RVA and the electromechanical delay between *septum* and posterior wall.

Although experimental investigations[28,29] and those carried out in adult population[30,31] show impairment of LV diastolic function, there are not enough studies to evaluate the function in the pediatric population. Tatengco *et al.*[5] estimated diastolic function in 24 children with chronic pacing from the RV and found damage in the maximum rate of ventricular filling, but not in other parameters such as the rapid ventricular filling, diastasis and atrial contraction. In our serie[27] no long-term involvement of this function is detected, so the absence of other pediatric studies makes us recommend its assessment in future research, with a longer evaluation.

Alternative pacing sites

To date, the alternative sites for ventricular pacing from the RV described are: mid-*septum,* inflow and outflow tracts of the RV (RVOT) septal region of the RVOT, bundle and para-Hisian regions. The RVOT has been one of the most studied, as it was initially used as an alternative site in cases with inadecuate pacing and sensing thresholds[32]. It constitutes a complex estructure, above limited by the pulmonary valve and at its lower end by the septal leaflet of the tricuspid valve, and is formed by the free wall, septal region and part of the anterior wall of the right ventricle (**Figure 3A**)[32]. The terminology: septal RVOT region is a false cognate, because the upper region is attached to the proximal ascending aorta and therefore is more related to it than to the LV. Furthermore, the posterior wall of the *conus arteriosus* (infundibulum) is too high and thin to achieve feasible pacing, plus obtaining high thresholds when pacing from this region. For these reasons only the lower septal region is considered as a true *septum*. Anatomically, this area is located below the supraventricular crest and contains septoparietal trabeculations, which are ideal regions to achieve stability in the active fixation electrodes (**Figure 3B**)[32].

The term RVOT is not always well defined in publications and is used to describe regions of the RV, as the infundibulum, the free wall, *septum* and adjacent apex-regions. However, it is important to differentiate sites within the RVOT, because the activation pattern and propagation of depolarization differ depending on the anatomical location of the electrode; not giving the precise location where it stimulates could in fact, explain the controversial results[33-36].

Since the first report of Durrer *et al.*[37], it is suggested that the septal regions of the LV are the first ventricular regions to be depolarized, which in theory suggests that if paced from the right areas of the *septum* near these regions, could be obtained a more physiological contractile pattern. A research in vitro[33] reflects how during the septal pacing (medial region),

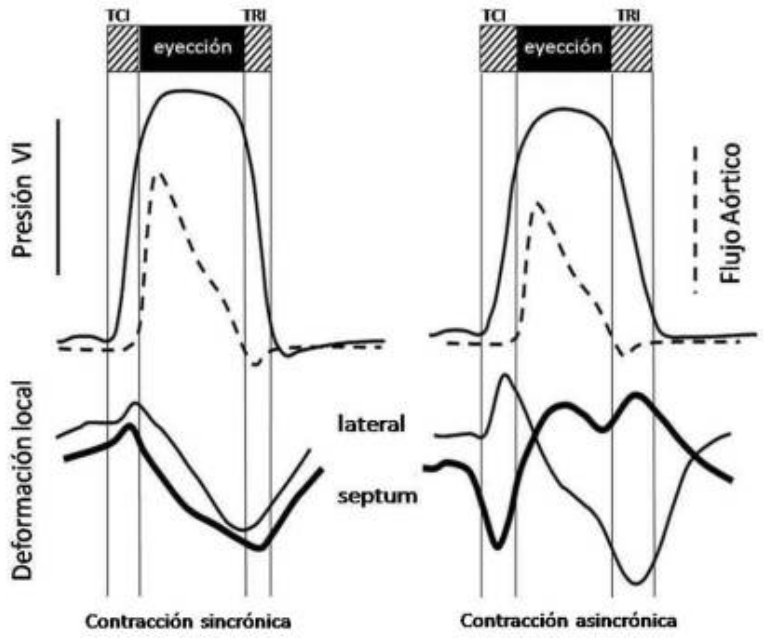

Figure 2. Effect of synchronous and asynchronous ventricular activation over LV pressure and the regional deformation. Asynchronous contraction produces paradoxical *septum* movement, slow increase in left ventricular pressures with reduction of ejection time. Adapted from Sweeney and Prinzen. Cir Arrhythm Electrophysiol. 2008; 1: 127-39[12], with permission. Acronyms in Spanish: *TCI*, isovolumetric contraction time; *TRI*, isovolumetric relaxation time; *VI*, left ventricle.

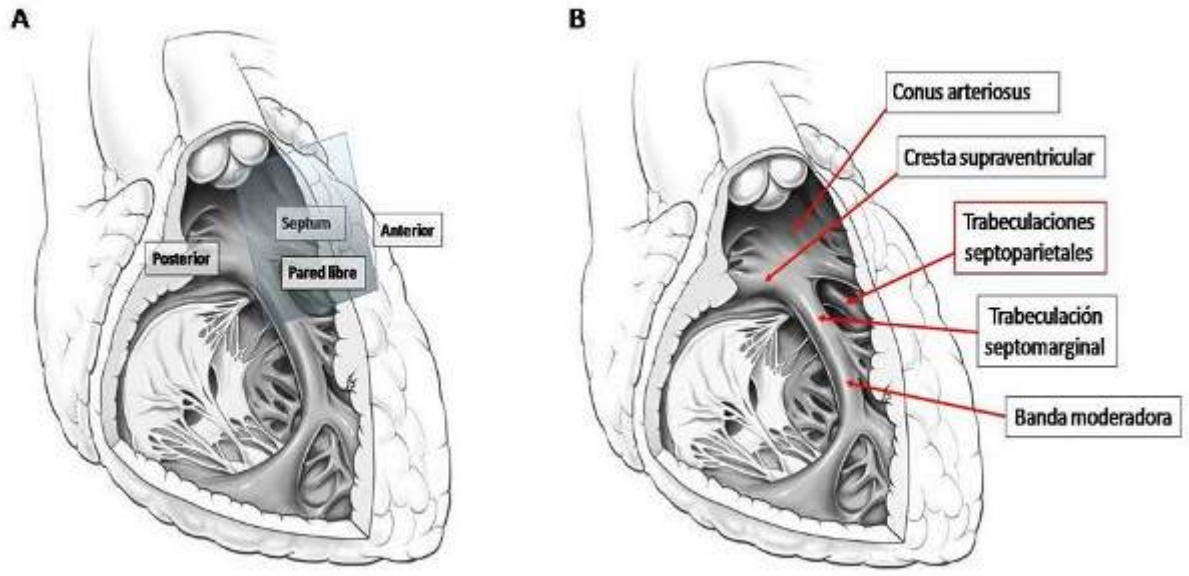

Figure 3. Cardiac anatomy where the RVOT stands. **A**. Electrophysiological view reflecting relations between the septal region and free and anterior walls of the RV. **B.** Anatomical view of septal region bordering structures. Adapted from Hillock and Mond. Europace.2012;14:28-35[32], with permission.

the *septum* is depolarized relatively early, but the activation wave generated spreads slowly through endocardial LV to belatedly reach its side wall. As a result, the distribution of systolic shortening is more heterogeneous in terms of time, space and breadth; mechanical dyssynchrony and discoordination rates increase, and hemodynamically the slope of dP/dt decreases and LV contractility can be reduced up to 30% compared to basal values[33].

Clinical evidence is still controversial regarding the benefits of septal pacing over conventional apical. Tse *et al*.[34] found that compared to RVA, pacing of the *septum* produces fewer perfusion defects and myocardial wall contractility, and therefore the expense of the left ventricular function is dimmed. Moreover, in a later study, the same group of authors[38] suggest that septal pacing could reverse the deleterious effect of chronic pacing from the RVA.

In a meta-analysis by Shimony*et al*.[35]were included 14 randomized studies and pacing from the RVA was compared (369 patients), to no apical (385 cases). It was demonstrated a favorable effect on ventricular function in patients with septal pacing, with further evaluation periods over 12 months and with LVEF ≤ 45%; however, they found no substantial differences in functional testing, quality of life or morbidity and death rate[35]. Meanwhile, Kypta *et al*.[36] found no superiority of conventional *septum* pacing over conventional apical in terms of LVEF, functional capacity and natriuretic peptide levels. Similarly, in a multicenter research[26] in the pediatric population, the authors report the same results in terms of inter- and intraventricular dyssynchrony and depressed systolic function obtained in patients paced from the RVA and the *septum.*

Although the inferiority of septal pacing regarding the apical has not been demonstrated, it has not become widespread in the pediatric patient due to: absence of randomized trials in this population showing clinical benefits, discrepancies in the results of research in the adult population and the technical difficulties to achieve the final electrode implantation in the desired septal region, due to the RVOT´s complex anatomy.

Alternative sites are the His and para-Hisian regions. In patients without distal conduction alterations, pacing from these regions induces a physiologically normal activation sequence and therefore, the damage associated with a dyssynchrony pattern[39] is prevented. Early clinical studies were published by Deshmukh *et al*.[39,40], who demonstrated the benefits of permanent His bundle pacing in 36 patients with

dilated cardiomyopathy, LVEF 23±11%, persistent atrial fibrillation and QRS <120 ms; after 42 follow-up months, managed survival of 29 patients and improvement in LVEF and clinical and hemodynamic parameters of left ventricular function. Meanwhile, Catanzariti *et al*.[41] evaluated the acute effects in 17 patients with His bundle pacing and 6 para-Hisian pacing; when compared to cases paced from the RVA, the first two groups maintained adequate levels of synchrony and absence of mitral regurgitation. Years later, this same grupo[42] reported the results of a long-term monitoring of patients with apical and bundle pacing, and after 34±11 follow-up months, the group paced from the His, compared to pacing from the RVA, showed preservation of LVEF (57.3 ± 8.5 vs. 50.1 ± 8.8%; p <0.001), lower incidence of mitral regurgitation (16.3 ± 12.4 vs. 22.5 ± 10.9%; p = 0.018) and no asynchrony rate[42] .

Despite the development and improvement of technical and specific catheters to achieve proper implementation of the His-bundle pacing, there are no studies for the pediatric population. The existence of a small Hisian area with the complexity of locating a permanent electrode in the trunk of the His-bundle and moreover, that this structure is involved in the pathogenesis of CAVB, both congenital and acquired (after surgery), and also that the block may be electrophysiologically infra-Hisian, preclude the application of this alternative pacing in pediatrics.

Left ventricular pacing

Based on the evidence that show dissimilar experimental[33,43] and clinical[26,27,44-47] research the left ventricle has been postulated as the optimal pacing site in the pediatric population. When the RVA is paced (**Figure 1D**) an early depolarization of this region takes place, leading to the rapid spread of an activation wave throughout the endocardium and in apex-base direction; as a result, the side wall and *septum* are synchronously activated while the base of the RV tends to be belatedly depolarized[43]. Furthermore, the pacing from the septal region of the LV (**Figure 1E**) produces a rapid and synchronous activation of the whole left ventricular endocardium, producing this pattern that more closely resembles that one physiological generated during driving, although the regions of the RV free wall are the last to be depolarized[43.]

Parameters of synchrony similar to physiological ones have been obtained from both sites, as the rate of global mechanical dyssynchrony (100-150 ms), in coordination and distribution of mechanical work, so the native ventricular asynchrony[33] is preserved. Other indicators, such as contractility, relaxation, myocardial oxygen consumption, myocardial perfusion and efficiency suffer no detriment and even there have been determined increase in septal perfusion with apical pacing[12,33]. Tomaske *et al*.[44] assessed the effects of chronic pacing from the RV and LV apex and in 25 children without structural heart disease. Although pacing from the LVA was associated with longer duration of pQRS, opposing to the right apical pacing, echocardiographic assessment showed no difference in terms of function and timing of the LV when compared with a group of healthy subjects[44]. Similarly, in another cohort study[45] were included 32 CAVB pediatric patients without structural heart disease and when compared the groups paced from the side wall of the LV with RVA it was estimated that the first preserved the shortening fraction (32.2±5.2 *vs.* 21.7± 6.0%; p <0.001) and the electromechanical *septum*-posterior wall delay (-16±14 vs. 338±20 ms, p <0.001)[45]. In other series[26,27] involving a larger number of cases, the results demonstrate the superiority of the left ventricular pacing over conventional regarding the preservation of synchrony and cardiac function, being equally stimulated from the *septum*, the sidewall or LVA.

The benefits of left ventricular pacing have been compared with those derived from biventricular pacing, and have proven to be effective especially when stimulated from the side wall of the LV. Vanagt *et al*.[46] describe the case of a 2 year patient with CAVB and HF by chronic pacing from the RVA, who they managed to resynchronize by implanting an electrode in the region of LVA. Also, Tomaske *et al*.[47], report improvement in ventricular function, dyssynchrony and adverse remodeling in children with chronic pacing of the RV, in whom the benefits of being stimulated from the LV appear just a month later.

Recommendations for pacing in pediatrics

The above shown evidence moves us to rethink what is the objective to be achieved in a pediatric patient who requires the implantation of a permanent pacemaker. Children often are treated at an early age, so they require pacing for several decades; Therefore, rather than stimulate, we must think of preserving ventricular function, being able to select the optimal site

in each of our patients.

The proper selection of the site and the pacing mode should take into account aspects such as age, growth curve, the type of cardiopathy, surgical correction already performed or to be performed, the state of the atrio-ventricular conduction, as well as short circuits and venous anomalies. It also seems reasonable to think that the sequence of activation should differ whether the patient has a disease or not, and even more if you consider the impact that involves long-term or secondary sequelae from a corrective surgery (eg: branch block). For this reason, it is recommended to select the pacing mode and site depending on the presence or absence of a structural disease (**Figure 4**).

Left ventricular pacing from the epicardium is sought in neonates, suckling and young children. It is common practice in our institution, the implantation of an electrode in the epicardial region of the LV by means of a left lateral thoracotomy, thus obtaining appropriate pacing and sensing thresholds and optimal aesthetic results. Other common access approaches are sternotomy or subxiphoid incisions.

In the case of older children and adolescents, it is generally accepted transvenous pacing, always avoiding to pace the RV free wall. Given the tolerance of pediatric population to chronic pacing from the RVA, endocardial electrode implantation is still recommended in this region. Though it does not show superiority, another useful variant would be to place the electrode at the level of the *septum*, and even more when the patient has a right bundle branch block after a heart disease correction. Similarly, a left ventricular pacing via coronary sinus could be performed from the endocardial access. In any variant it is advisable to perform routine echocardiographic evaluations. At present there are (MVP and AAIsafeR) algorithms[48] integrated to the generators

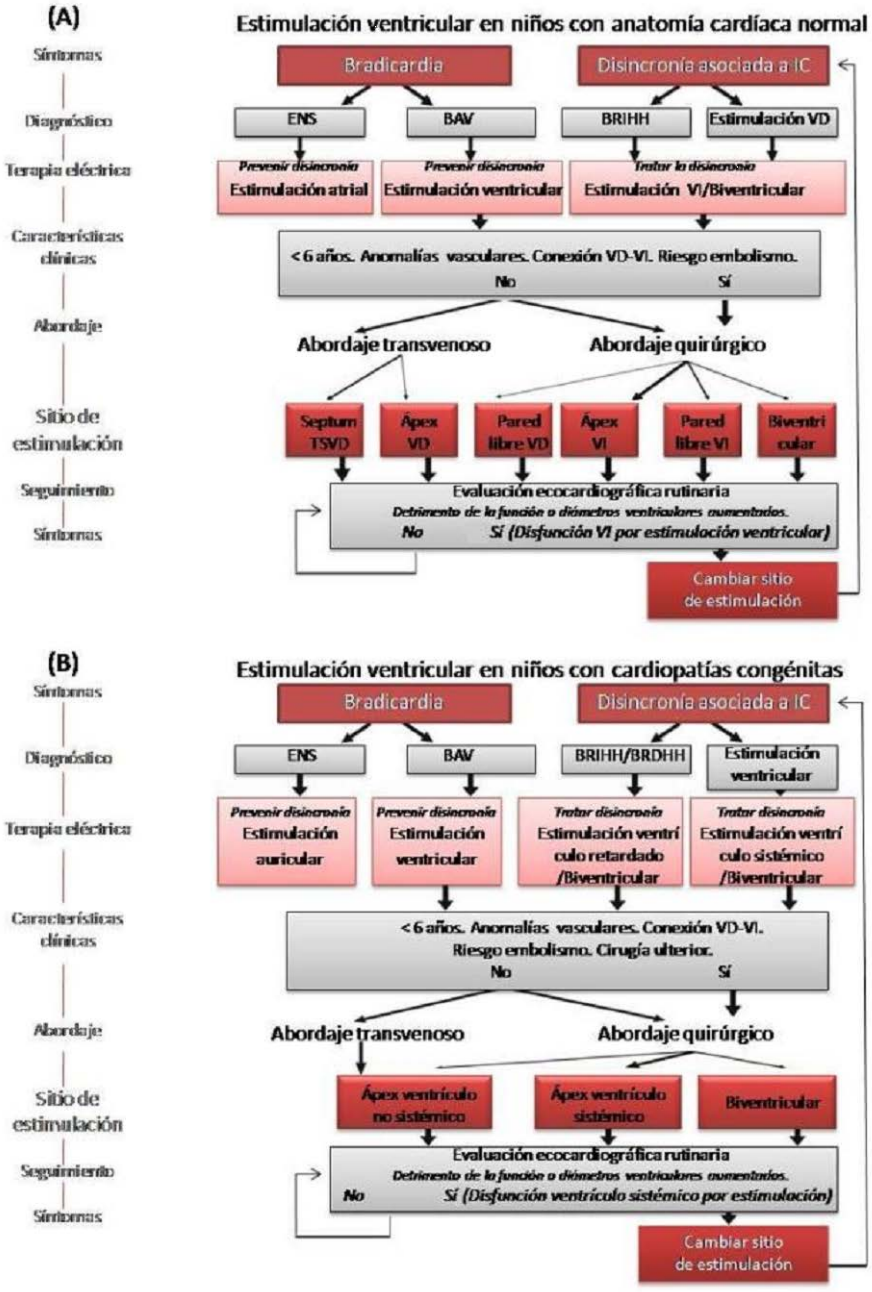

Figure 4. Recommendations for selecting the optimal pacing in pediatrics. **A**. Patients with normal cardiac anatomy. **B**. Patients with congenital heart disease. Adapted from van Geldorp *et al.* Heart Fail Rev 2011; 16: 305-14[1], with permission. Acronyms in Spanish: *BAV*, atrioventricular block; *BRDHH*, right bundle branch block; *BRIHH*, left bundle branch block; *ENS*, sick sinus syndrome; *IC*, heart failure; *TSVD*, right ventricular outflow tract; *VD*, right ventricle; *VI*, left ventricle.

that promote greater intrinsic ventricular activation times, without detecting adverse effects related to these pacing therapies.

CONCLUSIONS

Ventricular pacing site is the major determinant in the preservation or deterioration of synchrony and left ventricular function in the pediatric population. Though the LV is considered the optimal site, tolerance to the deleterious effects promoted by pacing from the RVA and widespread disuse of non-surgical techniques to pace LV, cause today´s preference for choosing the RV as the final pacing site.

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