Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ihj

Review Article

Physiological cardiac pacing: Current status

Asit Das [a,*], Dhiman Kahali [b]

[a] RMO-cum-Clinical Tutor, Department of Cardiology, IPGME&R and SSKM Hospital, Kolkata, India
[b] Senior Interventional Cardiologist, B. M. Birla Heart Research Centre, Kolkata, India

ARTICLE INFO

Article history:
Received 7 January 2016
Accepted 28 March 2016
Available online 6 April 2016

Keywords:
Physiological pacing
Direct His bundle pacing
Para-Hisian pacing
Ventricular septal pacing
Atrial septa pacing

ABSTRACT

Adverse hemodynamics of right ventricular (RV) pacing is a well-known fact. It was believed to be the result of atrio-ventricular (AV) dyssynchrony and sequential pacing of the atrium and ventricle may solve these problems. However, despite maintenance of AV synchrony, the dual chamber pacemakers in different trials have failed to show its superiority over single chamber RV apical pacing in terms of death, progression of heart failure, and atrial fibrillation (AF). As a consequence, investigators searched for alternate pacing sites with a more physiological activation pattern and better hemodynamics. Direct His bundle pacing and Para-Hisian pacing are the most physiological ventricular pacing sites. But, this is technically difficult. Ventricular septal pacing compared to apical pacing results in a shorter electrical activation delay and consequently less mechanical dyssynchrony. But, the study results are heterogeneous. Selective site atria pacing (atrial septal) is useful for patients with atrial conduction disorders in prevention of AF.

1. Introduction

From its first human implantation (October 8th, 1958 by Swedish Surgeon Ake Senning), the right ventricular (RV) apical pacing has saved millions of lives. But, within one decade, it was proved to be non-physiological as it causes several adverse hemodynamic effects. Contemporary thinking led to the assumption that pacing the atrium and ventricle sequentially may solve the problem of unsynchronized contraction. So, dual chamber cardiac pacing (DDD/R) was introduced as the "physiologic" pacing mode.

The term "physiological" was first used in Canadian Trial of Physiological Pacing (CTOPP) to reflect the terminology at the time of development of the trial.[1] However, despite maintenance of atrio-ventricular (AV) synchrony, the dual chamber pacemakers (DDD/R) in different randomized controlled trials (RCTs) have failed to show its superiority over single chamber RV apical pacing in terms of death, progression of heart failure (HF), and atrial fibrillation (AF).[1–3] This mysterious inability to show an advantage of physiologic DDD/R versus non-physiologic ventricular pacing may be explained by a factor common to all modes of ventricular pacing and also influencing short- and long-term cardiac pump function: ventricular asynchrony. Retrospective analysis of the Mode Selection Trial (MOST) suggests that the risks of HF hospitalization and AF can be directly linked to right ventricular apical (RVA) pacing burden (cumulative percent ventricular pacing) regardless of pacing mode.[2] This probably can be partially managed by manipulation of pacing modes

* Corresponding author.
E-mail address: dradascard@rediffmail.com (A. Das).
http://dx.doi.org/10.1016/j.ihj.2016.03.033

and timing cycle operation among patients with reliable AV conduction to minimize unnecessary ventricular pacing and preserve normal ventricular conduction. But, in patients with high presumed ventricular pacing burden (when ventricular pacing cannot be avoided and/or abnormal ventricular conduction is already present) pacing at alternate ventricular site(s) to attenuate the adverse effects imposed by ventricular desynchronization should be employed.

2. Ventricular pacing for AV conduction disorder

Most common indication for ventricular pacing is AV conduction disease. This AV disease can be at the level of AV node (nodal), at the His bundle (intra-Hisian) or below the level of His bundle (infra-Hisian). Determining the level of block is clinically important. A narrow QRS complex is most compatible with an AV nodal or intra-His problem. A wide QRS complex is most compatible with an infra-His problem. However, a wide QRS complex certainly may occur with AV nodal or intra-Hisian disease in presence of co-existent bundle branch block.[4] Normal PR interval (≤160 ms) of a conducted P wave indicates disease in the His bundle or His-Purkinje system and a PR of >300 ms indicates block in the AV node. His bundle escape rhythm typically has a rate of 45–60 beats per minute. So, in presence of third degree block, if the ventricular rate is greater than 50 bpm, the escape pacemaker is likely to be located high in the AV junction, and the site of block is likely to be in the AV node. In a patient with two-to-one AV block, improvement of conduction by atropine, beta agonists, or exercise suggests an AV nodal site of block. Carotid sinus pressure worsens the block in case of AV nodal block. Failure of conduction to improve with isoprenaline or atropine and paradoxical improvement with carotid sinus pressure suggest intra-His or infra-His block. In case of AV nodal block, there is no VA conduction. But, in case of intra- and infra-Hisian block, there may be presence of retrograde conduction. So, when a pacemaker is to be implanted for assumed or proven intra- or infra-His block, the operator has to consider the possibility of pacemaker syndrome or pacemaker-mediated tachycardia and choose the appropriate pacemaker and programming to prevent their occurrence. Multiple levels of AV block may coexist in the same patient, and they can produce a confusing ECG picture that is extraordinarily difficult to interpret without an intracardiac electrophysiology study.[4]

3. Adverse effects of RV apical pacing

RV apical pacing induces a slower myocyte-to-myocyte propagation of the electrical activation wave front throughout both the RV and left ventricle (LV), rather than rapid propagation through the His-Purkinje network. As a result, surface electrocardiograms exhibit a wide QRS complex and left bundle branch block pattern, characteristic of electrical dyssynchrony. This asynchronous electrical activation leads to asynchronous mechanical contraction which induces a spectrum of systolic and diastolic hemodynamic abnormalities. The MOST study showed that the patients with baseline lower ejection fraction (EF), history of myocardial infarction, and a worse New York Heart Association (NYHA) functional class are more likely to have these adverse events.[2] Batista and his colleagues have shown that even in patients with normal baseline ventricular function, conventional RV apical pacing leads to change in functional class, worsening in walk test, increased B type natriuretic peptide levels at the end of 2 years.[5] Over time, the sequelae of chronic pacing from the RV apex are a higher risk of development of left ventricular dysfunction, heart failure, AF, and death.[6–9] Interestingly, despite these provocative observations, clinical experience indicates that the majority of pacemaker patients tolerate chronic RVA pacing reasonably well. In the MOST study, only about 10% of patients had HF during follow-up.[2]

4. Physiological ventricular pacing

4.1. *Direct His bundle pacing*

Direct His bundle pacing (HBP) utilizes the native His-Purkinje conduction system and is supposed to be the most physiological ventricular pacing site for patients with AV nodal or intra-Hisian block. Direct HBP does not induce interventricular or intraventricular asynchrony or trigger the myocardial perfusion disorders described with RVA pacing as it produces ventricular contraction via the specific conduction system.[10] Direct HBP is accomplished with a steerable catheter (Selectsite), inserted into the right atrium via the subclavian vein, through which a dedicated bipolar, lumen less screw in, steroid-eluting, 4.1-Fr lead (Select Sure) is advanced into the area of triangle of Koch and mapping of the triangle of Koch is performed until the best near-field His bundle signal is recorded. This electrophysiologic mapping is guided by the quadripolar catheter previously positioned with the distal bipole on the His. Once the His signal has been recorded by means of the pacing lead, a clockwise turn is applied in order to fix the lead to the heart. Alternatively, it can be done with conventional active fixation leads. The safety and feasibility of HBP with conventional pacing leads have been shown in several studies.[11]

There are certain problems unique for the HBP with conventional active fixation pacing leads: (1) higher pacing threshold owing to the fibrous structure (less myocardium), (2) the close proximity of the tricuspid valve and its movements contribute to the greater instability of the lead, (3) low success rate.[10] Because the His-region block can become enlarged and encompass the lead site, an additional safety lead should be considered at the apex or right outflow tract to prevent asystole, especially in patients with pure His-bundle capture. This lengthens the surgical procedure time and results in a higher cost. These problems can be overcome by Para-Hisian pacing (PHP) rather than direct HBP. PHP involves simultaneous activation of the His bundle and ventricular septal myocardium. PHP is simpler and more reliable, seems to guarantee physiological ventricular activation of the high muscular part of the intraventricular septum, and also early invasion of the His-Purkinje conduction system, very similar to the activation that can be achieved by direct HBP.[11]

Direct HBP or selective HBP is defined as narrow paced QRS complex with concordance of QRS and T wave complexes with native QRS with identical pace-ventricular interval HV interval and widening of QRS complex at high output due to capture of ventricular fibers. PHP is evidenced by wider paced QRS duration than spontaneous QRS (but the duration must be at least 50 ms shorter than the QRS obtained with RV apical pacing and, in any case, not more than 120–130 ms with the electrical axis of the paced QRS concordant with the electrical axis of the spontaneous QRS) with significantly shorter pace-ventricular interval than HV interval of the original rhythm (with value close to zero) and narrowing of QRS complex with higher output.[12]

According to the theory of the longitudinal dissociation of the His bundle, the fibers ascribed to the right and left branches are histologically differentiated and isolated inside the trunk.[13] So, a bundle-branch block or complete block can be classified as central (His bundle) or peripheral (branches or Purkinje system) depending on whether or not they disappear with HBP. Three patterns of pacing are possible: (1) Pattern 1: Presence of latency and disappearance of bundle branch and complete AV block with normalization of QRS complex which indicates a central block, (2) Pattern 2: Absence of latency with the disappearance of bundle branch and complete AV block without normalization of QRS complex which indicates a 'fusion' caused by capture of the His bundle and the adjacent myocardium (PHP), (3) Pattern 3: Presence of latency and persistent bundle branch or complete infra-Hisian AV block indicates a peripheral block.[11] So, patients with patterns 1 and 2 paced QRS configuration are candidates for HBP or PHP and pattern 3 is not appropriate for this kind of pacing.

4.2. *Ventricular septal pacing*

Ventricular septal pacing should be considered for patients with infra-Hisian conduction block (Pattern 3) and in cases of failure to achieve direct HBP or PHP. In ventricular septal pacing, an active fixation lead is positioned at the septo-parietal trabeculation of the interventricular septum. The idea of septal pacing is based on the fact that the septal regions of the right ventricular outflow tract (RVOT) and mid RV are the first zones of the ventricle to depolarize, suggesting that pacing from these areas on the right side of the septum would achieve as normal a contraction pattern as possible. Harry Mond has developed a specially shaped stylet (Mond's stylet) for easier implantation of the lead into the interventricular septum.[14] He has described ECG features, radiological appearances, and implantation techniques of ventricular septal pacing in several studies.[15] Recently, Srivatsa has suggested another alternative technique of septal pacing which involves modification of Mond's stylet with more acute primary curve and less acute secondary curve and right ventriculogram in RAO projection with Swan-Ganz catheter during lead positioning.[16] However, this technique needs additional instrumentation.

Results of different trials comparing RV apical versus RV septal pacing are heterogeneous. Moreno and colleagues in a double-blind prospective randomized study have shown that after 1-year follow-up in persistently pacemaker-dependent patients, with no clinical evidence of severe congestive heart failure, midseptal ventricular lead placement is superior to the apical location in terms of clinical (6-minute walk) and functional (LVEF) parameters.[17] Using echocardiography as the ''gold standard'' to directly visualize and define the exact pacing sites and to examine the long-term impact of RV septal versus apical pacing on LV synchrony and function, Leung and colleagues have shown that long-term heterogeneous RV septal pacing may have more deleterious effects on LV function compared with apical pacing despite achieving a narrower QRS complex.[18] Several other studies also failed to prove the superiority of the RV septal pacing over the apical pacing. These clinical studies are flawed in that the leads were positioned in the RVOT and not necessarily septal.[19–21] More studies with positive results favoring ventricular septal pacing are needed. Even then, the detrimental effects of long-term RV apical are significant enough to suggest that it is high time to leave the RV apex.

At the present moment, absolute indication for RV apical positioning of the ventricular lead in dual chamber pacemaker is hypertrophic obstructive cardiomyopathy. RV apical pacing can also be considered appropriate for patients in whom presumed pacing burden is very low (i.e., paroxysmal excitation and/or conduction disease).

4.3. *LV pacing or biventricular pacing*

In hearts with normal ventricular conduction, LV pumping function is less adversely affected by pacing from most LV sites than by RVA pacing.[22] Studies have shown that pacing at the infero-apical LV septum and the epicardium of the LV apex yields LV pumping function that closely approximates function during normal ventricular conduction.[23] These results may be explained by rapid engagement of the specialized conduction systems in the LV wall near its ''break out'' site. Studies have shown that pre-existing ventricular dyssynchrony can be made worse by RVA pacing, with clinical consequences.[2] Left ventricular or biventricular (BiV) pacing should be used to correct pre-existing mechanical dyssynchrony associated with dilated cardiomyopathy and symptomatic HF, regardless of AV conduction status and independent of the need for bradycardia support. Sweeney has suggested LV pacing or BiV pacing or HBP as the optimum pacing site for the patients with high presumed pacing burden with baseline LV systolic dysfunction and/or mechanical dyssynchrony.[24] The BLOCK-HF trial has shown the superiority of BiV pacing over conventional RVA pacing in patients with AV block and left ventricular systolic dysfunction with NYHA class I, II, III heart failure.[25]

5. Atrial pacing for sinus node diseases

Atrial lead insertion during permanent pacemaker implantation is done for either symptomatic sinus node dysfunction (SND) or for maintenance of AV synchrony in a dual chamber pacemaker for AV conduction disease. Conventionally, it is placed in the right atrial appendage (RAA). But, the placement of right atrial (RA) lead in RRA had been challenged as inadequate and non-physiological in patients with SND, especially in presence of inter- and intra-atrial conduction delay as it has been shown to result in a higher incidence of

AF.[26] In addition to abnormalities at the sinus node, SND is associated with widespread structural and electrophysiological changes in the atria. The occurrence of AF after pacemaker implantation in SND is associated with an increased risk of stroke, systemic embolism, heart failure, and mortality.[27] Various factors such as bradycardia, delayed inter- and/or intra-atrial conduction, atrial tissue mass, atrial stretch, and the interaction with the autonomic nervous system may affect the occurrence of AF.

During sinus rhythm, the right and left atria are activated nearly simultaneously (within 50–80 ms). The spread of activation from one atrium to the other follows preferential pathways: (1) the high septal right atrium or Bachmann's bundle, (2) the limbus fossa ovalis, (3) the proximal coronary sinus (CS) musculature, and (4) the region of Koch's triangle with left posterior extension of the AV node.[28] The right atrium (RA) gets activated simultaneously over a wide area from the superior vena cava to low RA (from superior to inferior in all walls) with latest activation in low septal area. Left atrial (LA) activation during sinus rhythm is characterized by the presence of a consistent but variably complete line of conduction block that extends from the LA roof to the septal part of the mitral annulus.[29] This line of conduction block is due to collision of the 2 activation fronts: superior front through the Bachmann's bundle (BB) and inferior front through CS musculature.

6. Atrial conduction disorders

Atrial conduction disorders can be due to either intra- or inter-atrial conduction delay. Intra- and inter-atrial conduction disturbances are well-known factors predisposing to AF development and/or maintenance.[30] Two potential mechanisms produce atrial conduction disorders: (1) spatial dispersion of refractory periods or anisotropy resulting from scarce side-to-side electrical coupling, and (2) discrete fibrosis disrupting the arrangement of atrial muscle fiber bundles or to major ultrastructural abnormalities. The most common site for conduction delay in patients with intra-atrial conduction delay is Koch's triangle. The LA activation occurs predominantly from the activation wave front through Bachmann's bundle from the right atrium. So, the P wave morphology and P wave vector are similar to normal sinus rhythm. But, the duration of P wave is prolonged. P wave duration is traditionally measured in lead II and a value of >120 ms is abnormal. The ECG often shows a wide and notched P wave in lead II together with a wide terminal negativity in V1 commonly described as LA enlargement. Typically, the right intra-atrial conduction time is measured from the beginning of the P wave, or the intracardiac signal recorded in the upper part of the right atrium, to the onset of atrial depolarization in the Para-His bundle region. Its normal value is generally between 30 and 60 ms. Inter-atrial conduction time is measured from the beginning of the P wave or upper right atrium depolarization to the onset of LA depolarization recorded at the level of the distal CS. It is normally between 60 and 85 ms.[31]

Inter-atrial conduction delay is less common than intra-atrial conduction delay. It is due to conduction delay in the region of Bachmann's bundle (BB). In patients with inter-atrial block or BB block, due to block of superior wave front LA activation completely depends on ascending activation front originating from CS ostium leading to late activation of the left lateral LA roof.[32] This leads to widened ±P wave in the inferior leads. The direction of the negative terminal force vector, in leads II, III, and aVF, reflects delayed and caudo-cranial activation of the left atrium, probably from low inter-atrial connections at the level of Koch's triangle and CS. The delay from the beginning of the P wave (or the first deflection detected in the right atrium) to the deflection recorded in the distal CS averages 150 ms (range 120–180 ms).[33]

7. Physiological atrial pacing

Studies have shown that pacing atria from multiple sites in patients with atrial conduction disorder results in less incidence of AF. Multisite atrial pacing was introduced by Daubert et al., demonstrating that biatrial pacing from the high right atrium (HRA) and the distal CS is associated with low recurrence rates of atrial tachyarrhythmias in patients with severe inter-atrial conduction disturbances.[34] Saksena et al. suggested an alternative approach using pacing electrodes positioned in the HRA and at the CS ostium (“dual-site RA pacing”).[35] The 2 most investigated pacing sites within the inter-atrial septum are: (1) the antero-superior part (the BB region) or high atrial septum and (2) the infero-posterior portion near the CS ostium (the Koch triangle region) or low atrial septum. Spencer et al. showed that pacing in the inter-atrial septum at its anterior and superior region, close to Bachman's bundle, results in a symmetric activation of both the atria.[36] Several electrophysiological studies have shown that in patients with paroxysmal AF, single-site pacing at lower inter-atrial septum is more effective than biatrial or dual-site atrial pacing in the prevention of AF induction by shortening atrial activation times, and avoiding the undesirable prolongation of the inter-atrial conduction in patients with AF.[37]

Atrial septal pacing reduces incidence and recurrence of AF in patients with atrial conduction disorder by several mechanisms: (1) a very short inter-atrial conduction delay and a significant decrease in P wave duration; (2) a reduction in dispersion of atrial refractoriness; (3) a more homogeneous recovery of excitability and atrial activation; and (4) electrical atrial remodeling, with a gradual reduction in LA diameters and volume.[38]

7.1. *Lower atrial septal pacing*

Two large prospective randomized studies (EPASS and SAFE) have shown that low inter-atrial septal (IAS) pacing is superior to RAA pacing in preventing persistent or permanent AF in patients with SND and intra-atrial conduction delay.[39–40] For patients with SND without atrial conduction delay with history of AF, trial reports are controversial. Wang et al. have demonstrated that right low AS pacing in SND patients with paroxysmal AF who have a dual chamber pacemaker achieve better regional right and LA active mechanical properties and LA hemodynamic performance compared with those with

RAA pacing.[41] Inter-atrial electromechanical dyssynchrony is also reduced with right low IAS pacing. Padeletti et al. showed that rate-adaptive pacing at the triangle of Koch is more effective than RAA pacing in preventing symptomatic recurrences of paroxysmal AF in patients with sinus bradycardia and a history of AF.[42] However, 2 subsequent prospective, randomized studies in similar patient populations failed to demonstrate this superiority of IAS to conventional appendage pacing.[43–44]

7.2. *Upper atrial septal pacing*

Kugacka et al. have shown that single-site CS pacing causes echocardiographic pacemaker syndrome in the right heart because of simultaneous retardation of RA contraction and earlier ventricular activation, while single-site Bachmann's bundle pacing provides the best atrial contraction synchrony in patients with atrial conduction abnormalities, and has a comparable effect on global function to multisite atrial septal pacing.[45] Rothinger and his colleagues have demonstrated that the longest conduction time as a surrogate for the total atrial activation time is significantly shorter when pacing from the insertion site of Bachmann's bundle, as compared to pacing from the high right atrium or the CS ostium.[46] Bailin et al. in a randomized, multicenter trial evaluated the efficacy of conventional RAA pacing and of Bachmann bundle pacing in preventing progression to chronic AF as the primary end point and have shown that Bachmann bundle pacing is more effective in attenuating the progression of AF.[47]

For patients with SND without any history of AF in absence of atrial conduction delay, there is no difference between conventional RAA pacing and IAS pacing in prevention of AF (40–41). Hermida et al. have demonstrated better outcome of atrial septum pacing in patients with prolonged atrial, inter-atrial, and AV conduction in comparison to RAA pacing.[48] They have also shown that in patients with preserved but prolonged AV conduction mid atrial septal pacing above the CS os allow exclusive AAI pacing in more number of patients than RAA pacing. So, in patients with symptomatic trifascicular block atrial lead implantation in the mid atrial septum can be useful in prevention of AF. So, the trial reports in patients with SND with history of AF without atrial conduction delay are inconclusive with little in favor of BB pacing.

Choudhuri et al. have suggested that in patients with atrial conduction delay with SND, applying a universal septal/midline pacing technique to achieve atrial synchrony is not likely to be successful.[49] Low RA septal pacing may be effective only in patients with sick sinus syndrome with intra-atrial conduction delay. Patients with anterior conduction delay would not be expected to benefit from posterior septal acing; and in patients with posterior conduction delay, pacing the anterior septum is likely to accentuate the posterior conduction delay and enhance LA activation dispersion rather than be beneficial.

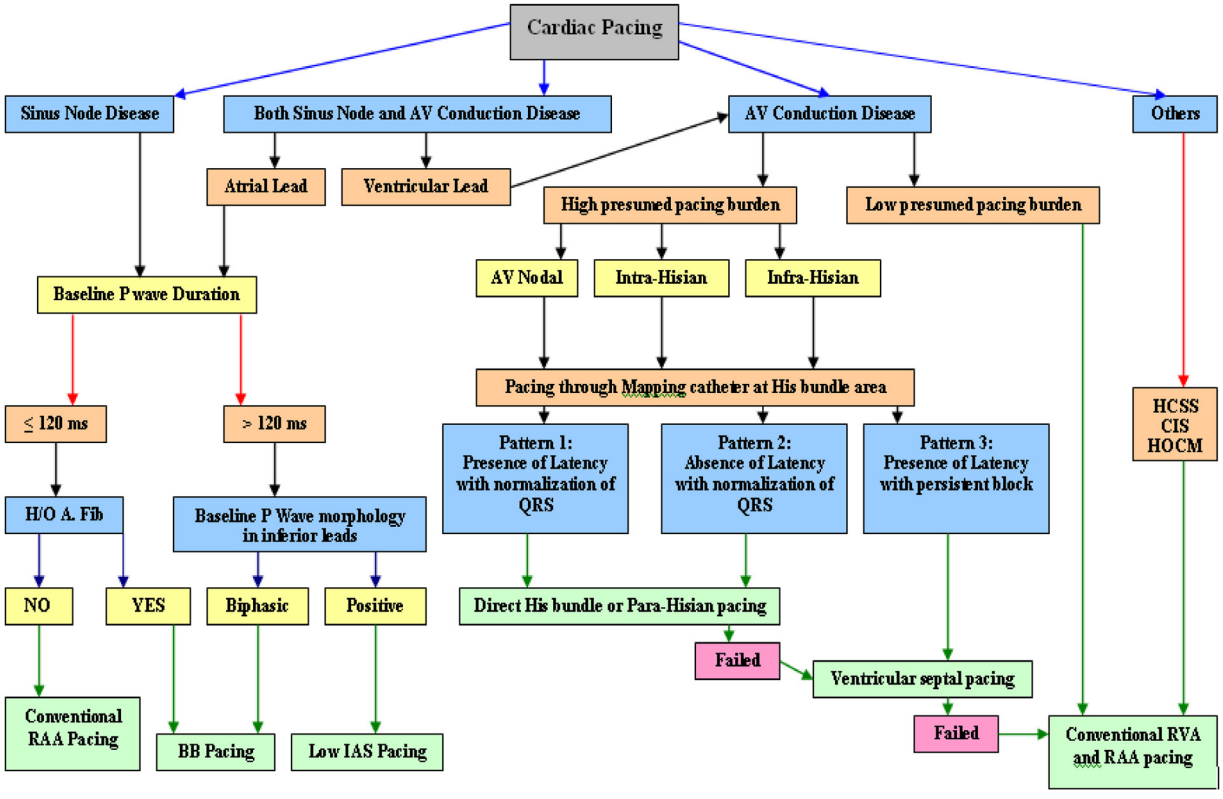

Fig. 1 – Proposed strategies for physiological pacing. A. Fib. = atrial fibrillation, AV = atrio-ventricular, BB = Bachmann's bundle, CIS = cardio-inhibitory syncope, H/O = history of, HCSS = hypersensitive carotid sinus syndrome, HOCM = hypertrophic obstructive cardiomyopathy, IAS = inter-atrial septum, RAA = right atrial appendage, RVA = right ventricular apical.

8. Conclusion

Fig. 1 summarizes the different proposed strategies of physiological cardiac pacing. Long-term adverse electromechanical and hemodynamics of RV apical pacing is a proven fact. Direct HBP or PHP is supposed to be the most physiological mode of pacing. It is ideal for patients with AV nodal disease or intra-His bundle disease. The process is tedious at the present moment with conventional tools and requires considerable expertise. But, it is ineffective for infra-Hisian disease where ventricular septal pacing should be performed. Conventional RV apical pacing can de considered appropriate for patients with very low presumed pacing burden.

Available data till date indicate that patients with SND with atrial conduction disease should receive the atrial lead at the inter-atrial septum (BB area for inter-atrial conduction delay and lower septum above the CS os for intra-atrial conduction delay). For patients with SND with history of AF, the upper atrial septum near BB area is the preferred site for pacing. For patients without atrial conduction disorder and without history of AF, the RAA is the suitable site for atrial pacing.

However, these various novel approaches to pacing have not yet been fully investigated in large RCTs. Several RCTs have shown that preservation of normal ventricular conduction by avoiding unnecessary RVA pacing reduces the risk of AF, HF, and death during pacemaker and ICD therapy.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiological pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. *N Engl J Med*. 2000;342:1385–1391.
2. Lamas GA, Lee KL, Sweeney MO, et al. Ventricular pacing or dual chamber pacing for sinus node dysfunction. *N Engl J Med*. 2002;346:1854–1862.
3. Toff WD, Camm AJ, Skehan JD. for the United Kingdom Pacing and Cardiovascular Events Trial (UKPACE) Investigators. Single chamber versus dual-chamber pacing for high-grade atrioventricular block. *N Engl J Med*. 2005;353:145–155.
4. Josephson ME. *Clinical Cardiac Electrophysiology: Techniques and Interpretations*. 4th ed. LWW Pub; 2002:93–113.
5. de Sa LAB, Rassi S, Andery M, et al. Is conventional cardiac pacing harmful in patients with normal ventricular function? *Arq Bras Cardiol*. 2013;101:545–553.
6. Tantengco MV, Thomas RL, Karpawich P. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. *J Am Coll Cardiol*. 2001;37:2093–2100.
7. Nielsen JC, Andersen HR, Thomsen PE, et al. Heart failure and echocardiographic changes during long term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation*. 1998;97:987–995.
8. Sweeney MO, Hellkamp AS, Ellenbogen KA, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation*. 2003;107:2932–2937.
9. Andersen HR, Thuesen L, Bagger JP, et al. Prospective trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet*. 1994;344:1523–1528.
10. Catanzariti D, Maines M, Cemin C, Broso G, Marotta T, Vergara G. Permanent direct His bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An intrapatient acute comparison study. *J Interv Card Electrophysiol*. 2006;16:81–92.
11. Barba-Pichardo R, Moriña-Vázquez P, José Venegas-Gamero JM, Herrera-Carranza M. Permanent His-bundle pacing: seeking physiological ventricular pacing. *Europace*. 2010;12:527–533.
12. Cantù F, De filippo P, Cardano P, De luca A, Gvazzi A. Validation of criteria for selective His bundle and Para-Hisian permanent pacing. *Pacing Clin Electrophysiol*. 2006;29:1326–1333.
13. El-Sherif N, Amay YLF, Schonfield C, et al. Normalization of bundle branch block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic his bundle. *Circulation*. 1978;57:473–483.
14. Mond HG, Hillock RJ, Stevenson IH, McGavigan AD. The right ventricular outflow tract: the road to septal pacing. *Pacing Clin Electrophysiol*. 2007;30:482–491.
15. McGavigan AD, Roberts-Thompson KC, Mond HG, et al. Right ventricular outflow tract pacing: radiographic and electrocardiographic correlates of lead position. *Pacing Clin Electrophysiol*. 2006;29:1063–1068.
16. Srivatsa SS. Finding the sweet spot for non-apical RV pacing. *J Invasive Cardiol*. 2014;26:140–147.
17. Molina L, Sutton R, Moreno G, et al. Medium-term effects of septal and apical pacing in pacemaker-dependent patients: a double-blind prospective randomized study. *PACE*. 2014;37:207–214.
18. Ng ACT, Allman C, Leung DY, et al. Long-term impact of right ventricular septal versus apical pacing on left ventricular synchrony and function in patients with second- or third-degree heart block. *Am J Cardiol*. 2009;103:1096–1101.
19. Mera F, DeeLurgio DB, Patterson RE, Merlino JD, Merlino JD, Wade ME, León AR. A comparison of ventricular function during high right ventricular septal and apical pacing after his-bundle ablation for refractory atrial fibrillation. *Pacing Clin Electrophysiol*. 1999;22:1234–1239.
20. Stambler BS, Ellenbogen KA, Zhang X, et al. Right ventricular outflow versus apical pacing in paced patients with congestive heart failure and atrial fibrillation. *J Cardiovasc Electrophysiol*. 2003;14:1180–1186.
21. Gong X, Su Y, Pan W, et al. Is right ventricular outflow tract pacing superior to right ventricular apex pacing in patients with normal cardiac function? *Clin Cardiol*. 2009;32:695–699.
22. Puggioni E, Brignole M, Gammage M, et al. Acute comparative effect of right and left ventricular pacing in patients with permanent atrial fibrillation. *J Am Coll Cardiol*. 2004;21:234–238.
23. Vanagt WY, Verbeek XA, Delhaas T, et al. The left ventricular apex is the optimal site for pediatric pacing: correlation with animal experience. *Pacing Clin Electrophysiol*. 2004;27:837–843.
24. Sweeney MO, Prinzen FW. A new paradigm for physiologic ventricular pacing. *J Am Coll Cardiol*. 2006;47:282–288.
25. Curtis AB, Adamson PB, Chung E, et al. Biventricular versus right ventricular pacing in patients with AV block (BLOCK HF): clinical study design and rationale. *J Cardiovasc Electrophysiol*. 2007;18:965–971.

26. Daubert JC, Pavin D, Jauvert G, et al. Intra- and interatrial conduction delay: implications for cardiac pacing. *Pacing Clin Electrophysiol.* 2004;27:507–525.
27. Tse HF, Lau CP. Prevalence and clinical implications of atrial fibrillation episodes detected by pacemaker in patients with sick sinus syndrome. *Heart.* 2005;91:362–364.
28. De Ponti R, Ho SY, Salerno-Uriarte JA, et al. Electroanatomic analysis of sinus impulse propagation in normal human atria. *J Cardiovasc Electrophysiol.* 2002;13:1–10.
29. Markides V, Schilling RJ, Ho SY, et al. Characterization of left atrial activation in the intact human heart. *Circulation.* 2003;107:733–739.
30. Papageorgiu P, Monahan K, Boyle NG, et al. Site-dependent intra-atrial conduction delay: relationship to initiation of atrial fibrillation. *Circulation.* 1996;94:384–389.
31. Legato MJ, Bull MB, Ferrer MI. Atrial ultrastructure in patients with fixed intra-atrial block. *Chest.* 1974;65:252–261.
32. Daubert J-C, Pavin D, Jauvert G, et al. Intra- and interatrial conduction delay: implications for cardiac pacing. *PACE.* 2004;27:507–525.
33. Cosio FG, Martin-Penato A, Pastor A, et al. Atrial activation mapping in sinus rhythm in the clinical electrophysiology laboratory: observation during Bachmann's bundle block. *J Cardiovasc Electrophysiol.* 2004;15:524–531.
34. Daubert C, Gras D, Beder V, et al. Resynchronisation atriale permanente par la stimulation biatriale synchrone pour le traitement préventif du flutter auriculaire associé à un bloc interauriculaire de haut degré. *Arch Mal Cœur Vaiss.* 1994;87:1535–1546.
35. Daubert C, Mabo P, Berder V. Arrhythmia prevention by permanent atrial resynchronization in advanced interatrial block. *Eur JCPE.* 1994;1:35–44.
36. Saksena S, Prakash A, Hill M, et al. Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. *J Am Coll Cardiol.* 1996;28:687–694.
37. Spencer WH, Zhu DW, Markowitz T, Badruddin SM, Zoghbi WA. Atrial septal pacing: a method for pacing both atria simultaneously. *Pacing Clin Electrophysiol.* 1997;20:2739–2745.
38. Padeletti L, Pieragnoli P, Ciapetti C, et al. Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. *Am Heart J.* 2001;142:1047–1055.
39. Noguchi H, Kumagai K, Tojo H, et al. Effect of Bachmann's bundle pacing on atrial fibrillation: electrophysiologic assessment. *Clin Cardiol.* 2004;27:50–53.
40. Verlato R, Botto GL, Massa R, et al. Efficacy of low interatrial septum and right atrial appendage pacing for prevention of permanent atrial fibrillation in patients with sinus node disease: results from the electrophysiology guided pacing site selection (EPASS) study. *Circ Arrhythm Electrophysiol.* 2011;4:844–850.
41. Lau CP, Tachapong N, Wang CC, et al. Septal Pacing for Atrial Fibrillation Suppression Evaluation Study Group: prospective randomized study to assess the efficacy of site and rate of atrial pacing on long-term progression of atrial fibrillation in sick sinus syndrome: Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) study. *Circulation.* 2013;128:687–693.
42. Wang M, Siu1 C-W, Lee KLF, et al. Effects of right low atrial septal vs. right atrial appendage pacing on atrial mechanical function and dyssynchrony in patients with sinus node dysfunction and paroxysmal atrial fibrillation. *Europace.* 2011;13:1268–1274.
43. Padeletti L, Pieragnoli P, Ciapetti C, et al. Randomized cross-over comparison of right atrial appendage pacing versus inter-atrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. *Am Heart J.* 2001;142:1047–1055.
44. Hermida JS, Kubala M, Lescure FX, et al. Atrial septal pacing to prevent atrial fibrillation in patients with sinus node dysfunction: results of a randomized controlled study. *Am Heart J.* 2004;148:312–317.
45. Dabrowska-Kugacka A, Lewicka-Nowak E, Ruciński P, et al. Single-site Bachmann's bundle pacing is beneficial while coronary sinus pacing results in echocardiographic right heart pacemaker syndrome in brady-tachycardia patients. *Circ J.* 2010;74:1308–1315.
46. Roithinger FX, Abou-harb M, Pachinger O, et al. The effect of the atrial pacing site on the total atrial activation time. *PACE.* 2001;24:316–322.
47. Bailin SJ, Adler S, Giudici M. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. *J Cardiovasc Electrophysiol.* 2001;12:912–917.
48. Hermida J-S, Carpentier C, Kubala M, et al. Atrial septal versus atrial appendage pacing: feasibility and effects on atrial conduction, interatrial synchronization, and atrioventricular sequence. *PACE.* 2003;26:26–35.
49. Choudhuri I, Krum D, Agarwal A, et al. Bachmann's bundle and coronary sinus ostial pacing accentuate left atrial electrical dyssynchrony in an acute canine model. *J Cardiovasc Electrophysiol.* 2014;25:1400–1406.