REVIEW ARTICLE

Adverse Consequences of Right Ventricular Apical Pacing and Novel Strategies to Optimize Left Ventricular Systolic and Diastolic Function

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Abstract: Several studies have focused on the deleterious consequences of Right Ventricular Apical (RVA) pacing on Left Ventricular (LV) function, mediated by pacing-induced ventricular dyssynchrony. Therapeutic strategies to reduce the detrimental consequences of RVA pacing have been proposed, that includes upgrading of RVA pacing to Cardiac Resynchronization Therapy (CRT), alternative Right Ventricular (RV) pacing sites, minimal ventricular pacing strategies, as well as atrial-based pacing. In developing countries, single chamber RV pacing still constitutes a majority of cases of permanent pacing, and assessment of the optimal RV pacing site is of paramount importance. In chronically-paced patients, it is crucial to maintain as close and normal LV physiological function as possible, by minimizing ventricular dyssynchrony, reducing the chances for heart failure and other complications to develop. This review provides an analysis of the deleterious immediate and long-term consequences of RVA pacing, and the most recent available evidence regarding improvements in pacing options and strategies to optimize LV diastolic and systolic function. Furthermore, the place of advanced echocardiography in the identification of patients with pacing-induced LV dysfunction, the potential role of a new predictor of LV dysfunction in RV-paced subjects, and the long- term outcomes of patients with RV septal pacing will be explored

Keywords: Right ventricular, apical pacing, ventricular dyssynchrony, cardiac resynchronisation therapy, systolic, diastolic.

1. INTRODUCTION

Permanent cardiac pacing continues to be the most effective therapy for patients with high-degree atrioventricular block and sick sinus syndrome [1]. The RV apex has been the conventional site of pacemaker implantation since the early days of pacing. RVA pacing is generally very-well tolerated and effective. However, dyssynchronous contractility associated with RVA pacing can have detrimental effects on LV function, potentially resulting in myocardial perfusion abnormalities, atrial fibrillation and heart failure [2]. The latter can be attributed to the abnormal mechanical and electrical activation pattern of the ventricles caused by RVA pacing. The above observations have propelled further interest in identifying alternative pacing sites and strategies that can optimize LV contraction. To date, the Right Ventricular Outflow Tract (RVOT) has been the most extensively studied of the Right Ventricular Non-apical (RVNA) pacing sites. The mid-septum, upper-septum, and septal his-bundle are some of the other RVNA pacing sites that have been proposed. Alternatively, the upgrading of RV apical pacing to CRT, minimal ventricular pacing strategies, and

atrial-based pacing have also been suggested as potential therapeutic options to minimize LV dyssynchrony arising from RVA pacing [3]. In this paper, we detail the detrimental acute and long-term consequences of RV apical pacing and its hemodynamic effects, with specific highlight on the role of RVA pacing-induced ventricular dyssynchrony. The impact of RVA pacing on left ventricular diastolic function in particular will also be discussed. Furthermore, we will analyse the most recent data regarding new alternate pacing strategies for subjects with an indication for permanent pacemaker, including CRT and alternative RV pacing sites, to optimise and preserve left ventricular function. Finally, the long-term outcomes of patients with RV septal pacing, the potential role of a novel predictor of LV dysfunction in RV-paced patients, and the utility of the latest echocardiography techniques to identify patient with pacing-induced left ventricular dysfunction will be highlighted.

2. OVERVIEW OF THE PATHOPHYSIOLOGICAL CONSEQUENCES AND PITFALLS OF RVA PACING

RVA pacing results in non-physiological activation of the left ventricle, leading to adverse clinical outcomes. Hence, alternative pacing sites, including the RVOT, the high-RV septal region, Bi-ventricular (BiV) pacing, or His Bundle Pacing (HBP), have been explored for a better physiological electromechanical coupling of the ventricles. The detrimental

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effects of RVA pacing results from anomalous pattern of electrical and mechanical activation of the ventricles induced by this method of pacing. RVA pacing results in mechanical dyssynchrony, reduced myocardial blood flow, and depressed Left Ventricular Ejection Fraction (LVEF) [4]. Long-standing ventricular dyssynchrony induced by long-term endovenous RVA pacing leads to adverse outcomes of LV remodeling, dilatation, asymmetrical hypertrophy, and reduced exercise tolerance. During this method of pacing, there is propagation of electricity through the myocardial tissue, as opposed to the His-Purkinje conduction system. This results in a slower propagation of the electrical activity, thereby inducing an activation pattern of the myocardium comparable to Left Bundle Branch Block (LBBB). It is crucially important to emphasize the differentiation between pacing-induced LBBB and intrinsic LBBB. Varma N showed that RVA pacing simulated LBBB in the normal left ventricle but in heart failure, RVP induced greater conduction delays than LBBB, enhanced by accompanying conduction disease, and that these variations may contribute to RVP's mixed clinical effects [5]. Another paper by Varma N demonstrated that RVP may aggravate or resolve LBBB-induced conduction problems at one or more level, and that its avoidance versus integration during CRT depends on its electrical action in any particular individual [6]. On the other hand, the mechanical pattern of activation of the left ventricle is also subject to alterations during RVA pacing. The pattern and onset of mechanical contraction are both modified as a result of this pacing method. The resultant effects are alterations in cardiac metabolism, hemodynamics, remodeling, as well as mechanical ventricular function [7-23] (Table **1**). Badke *et al.* demonstrated that apical pacing is

associated with a reduced rate of change in LV pressure, and a dyssynchronous ventricular contraction pattern, leading to asynchronous myocardial contraction and a corresponding reduction in the stroke volume. The mismatch between the relaxation of early and late-contracting myocardial areas results in a reduction in the filling time of the LV [8]. In their study using speckle-tracking analysis, Tops *et al.* demonstrated that permanent RVA pacing results LV dyssynchrony in 57% of patients, with a deterioration of LV systolic function and New York Heart Association (NYHA) functional class. Therefore, RVA pacing results in ventricular dyssynchrony, with consequent systolic and diastolic impairment of ventricular function [9]. In addition to the hemodynamic consequences of ventricular dyssynchronisation, long-term RVA pacing can also result in permanent structural changes in the myocardium, resulting in adverse LV remodeling. Furthermore, other parameters that all seem to contribute to the pathophysiological effects of RVA pacing are left atrial remodeling, functional mitral regurgitation, and abnormalities in regards to myocardial coronary perfusion [10]. The acute effects of RVA pacing on LV twist and synchrony result in an asynchronous patterns of left ventricular contraction, leading to an impaire +d LVEF. Over the recent years, it has been shown that RVA pacing can lead to cardiac failure, resulting in the hospitalization or death in patients with normal and depressed LV function. LVEF has importantly been shown to be closely related to the entity of LV twist [24]. From our search, the best study analysing the acute effects of RVA pacing on LV twist and synchrony was performed by Matsuoka *et al.* using 2D-ultrasound speckle-tracking imaging. In this study, it was successfully demonstrated that RVA pacing reduces apical and basal LV rotation

Table 1. Acute and Long-term effects of RV apical pacing.

Potential Harmful Effects	Pathophysiology	Clinical Studies
Alterations in electrical and mechanical activation	Intrinsic electrical and mechanical activation are deranged	Prinzen FW *et al.* 1999 [9]
		Vassallo JA *et al.* 1986 [10]
		Rodriguez LM *et al.* 2003 [11]
		Auricchio A *et al.* 2004 [12]
		Badke FR *et al.* 1980 [6]
Metabolism	Changes in oxygen demand and myocardial perfusion	Prinzen FW *et al.* 1990 [13]
		Skalidis EI *et al.* 2001 [14]
		Tse HF *et al.* 1997 [15]
Remodeling	Asymmetric ventricular hypertrophy and dilatation, functional MR	Karpawich PP *et al.* 1999 [16]
		Van Oosterhout MF *et al.* 1998 [17]
		Vernooy K *et al.* 2006 [18]
		Barold SS *et al.* 2005 [8]
		Maurer G *et al.* 1984 [19]
Mechanical function	Intraventricular and interventricular mechanical dyssynchrony, changes in myocardial strain	Tops *et al.* 2007 [7]
		Prinzen FW *et al.* 1999 [9]
		Kass DA *et al.* 2008 [20]
Hemodynamic consequences	Increased Left ventricular filling pressures, Reduced Cardiac output	Lieberman R *et al.* 2006 [21]

and induces LV apical-basal rotation delay, resulting in impaired LV twist [25]. However, although the study data demonstrated that RVA pacing reduces LV rotation, twist and untwist, and induces LV apical-basal rotation delay, long-term clinical follow-up trials of RVA-paced or CRT patients are needed to assess the clinical applications of LV twist and LV untwist. In another prospective study, it was also demonstrated using real-time 3D-echocardiography, that acute RVA pacing induces LV mechanical dysynchrony and acutely impairs LV function in sick sinus syndrome patients [26].

3. RVA PACING OUTCOMES FROM CONDUCTED STUDIES

Clinical studies attempting to demonstrate the deleterious effects of RVA pacing can be categorized according to the indication for pacemaker implantation or by the pacing mode. In their study, Andersen *et al.* [27] investigated 225 patients with SND by comparing VVI to AAI pacing, discovering a much higher cardiovascular mortality, incidence

of heart failure (HF) and NYHA functional class in the ventricular pacemaker group. On the other hand, the study by Nielsen *et al.* [28] showed that dual-chamber pacing is associated with enlargement of the left atrium compared to atrial pacing alone. These findings point to the plausible explanation that one of the detrimental consequence of RV pacing may be increased atrial pressure that results in atrial remodeling, potentially increasing the risk of atrial fibrillation (AF). Studies that focused on DDD *vs.* VVI-only pacing in patients with AV block [29], or patients with both AV block and SND [30], led to the hypothesis that RVA pacing may have adverse outcomes. It was expected that DDD pacing would be beneficial over RVA-only (VVI) pacing owing to the maintenance of AV synchrony, resulting in a decrease in the incidence of HF, cardiovascular mortality, AF and stroke. In these studies, it was observed that only the incidence of AF was significantly reduced, DDD pacing being questionable with regards to the importance of maintaining AV synchrony on heart failure and mortality (Table **2**). A subgroup analysis of the trial by Sweeney *et al.* among patients with QRS less than 120 milliseconds threw light on

Table 2. Studies examining RV pacing and outcomes.

Author	Study Population	Basal Disease	Treatment Group	Sample Size	Mortality	HF	AF	QRS	Follow- up
Andersen *et al.* 1997 [27]	225	SSS	AAI *vs.* VVI	AAI (n=110) VVI (n=115)	↑ VVI	↑ VVI	↑ VVI	N/A	Intermediate - mean 3.3 years
Connolly *et al.* 2000 [30]	2568	Symptomatic bradycardia	VVI *vs.* DDD	VVI (n=1284) DDD (n=1284)	↔	↔	↑	N/A	Intermediate - mean 3 years
Nielsen *et al.* 2003 [28]	177	SSS	AAI *vs.* DDD-l AV *vs.* DDD-s AV Delay	AAI (n = 54) DDD with a short AV delay (n = 60) (DDDR-s) DDD with a fixed long AV delay (n = 63) (DDDR-l).	↔	N/A	↑with RV pacing burden	Included only normal QRS duration	Intermediate - mean 2.9 years
Sweeney *et al.* 2003 [29]	1339	SND	VVI *vs.* DDD in SND	DDD (n = 707) VVIR (n = 632)	↔	↑with RV pacing burden	↑with RV pacing burden	Included only normal QRS duration	Intermediate - median 2.7 years
Wilkoff *et al.* 2002 [31]	506	Life-threatening ventricular arrhythmia requiring ICD	VVI-40 ICD *vs.* DDD-70 ICD	VVI-40 (n = 256) DDD-70 (n = 250)	↑with RV pacing burden	↑with RV pacing burden	↑	Prolonged QRS (LBBB) pacing worse	short term – median 0.7 years

SSS=Sick Sinus Syndrome.
AV= Atrioventricular
SND= Sinus Node Dysfunction.
ICD = Implantable Cardioverter Defibrillator.

a possible reason for the negative outcomes of these studies [29], demonstrating a strong association between RV pacing and the risk of HF and AF in both the DDD and VVI groups. The similar increases in HF and AF rates with DDD and VVI-only pacing supports the fact that maintaining AV synchrony does not translate into a risk reduction in either of them. On the contrary, it was noted that the RVA pacingburden outweighed any benefit of AV synchrony in the DDD group, and was therefore the main driver with regards to the negative trial result. The DAVID trial further reinforced the association between RV pacing and adverse cardiovascular outcomes [31]. After 1 year follow-up period, the combined endpoint of hospitalization for HF or death was significantly higher in the DDD - 70 group (26.7%) as opposed to the VVI - 40 group (16.1%). The difference in backup rate between the two groups resulted in a significant difference in the burden of RV pacing (60% *vs.* 3%). A right-ventricular pacing dose-dependent positive relationship with adverse cardiovascular events was well noted, in keeping with the findings from the MOST trial [32]. A systematic review and meta-analysis by Hussain *et al.* highlighted the concept that baseline LV function can possibly predict which patients will develop pacemaker-induced cardiomyopathy (PICM). This meta-analysis clearly demonstrated that in subjects with a baseline impaired LVEF of <40 % and requiring long term RV pacing, the increased pacing burden from RVA pacing is associated with a deterioration in LV function compared to RVNA pacing, hence proving the detrimental outcome of RVA pacing in patients with a baseline impaired LV function, which in the long-term can potentially result in clinically evident PICM. The latter contributes not insignificantly to the burden of disease in patients post pacemaker implantation and requires a significant change from conventional practice [33]. Furthermore, Shimony *et al.* conducted a systematic review and meta-analysis of 13 randomized-controlled trials and discovered RVNA pacing to result in an improved LVEF as opposed to RVA pacing at the end of the follow-up period. The authors concluded that after chronic pacing, RVNA pacing results in a higher LVEF than RVA pacing, reinforcing the concept that an increased pacing burden with RVA pacing is a risk factor for the development of PICM. Despite the fact that this finding is encouraging, its clinical significance is relatively uncertain, because current data available for other endpoints other than LVEF are so far limited. One of the main conclusions that can be drawn from this meta-analysis by Shimony *et al.* is that a follow-up period of over 1 year is needed to start appreciating the differences in LVEF between apical and non-apical pacing sites [34]. Yet another high-powered study by Merchant *et al.* on the incidence and time course for the development of heart failure with high-burden of RVA pacing, showed that patients with a diagnosis of complete AV block and thus presumed to have a higher burden of right ventricular pacing, experienced an increased risk of new-onset HF after pacemaker implantation compared with those without AV block. The authors suggested that better tools are needed to identify patients at high risk of developing HF in the setting of RV pacing and to determine whether these patients benefit from upfront biventricular pacing [35].

4. IMPACT OF RVA PACING ON LV DIASTOLIC FUNCTION AND IN PATIENTS WITH PRESERVED AND IMPAIRED LV FUNCTION

RVA pacing can lead to LV systolic dysfunction and heart failure even in those without pre-existing systolic dysfunction, most likely secondary to RVA pacing-induced systolic dyssynchrony. Despite the fact that LV diastolic function is an equally important entity of the cardiac cycle, there has so far been limited data on the effects of RVA pacing on diastolic function, and how this relates to changes in systolic function. Fang *et al.* demonstrated the adverse impact of RVA pacing on LV diastolic function in patients with preserved LVEF, occurring mainly in those with pre-existing LV diastolic dysfunction [36]. In another study, it was shown that both RV septal and apical pacing sites adversely affect LV mechanical synchrony. It was, however, specifically demonstrated that only the apical and not the septal site affects LV synchrony at 1 year, with an associated increase in LV filling pressure, leading to the conclusion that better LV synchrony and diastolic function are achieved in the case of septal as opposed to RVA permanent pacing [37]. On the contrary though, Mitov *et al.* showed that 1 year of pacemaker stimulation from the RVOT, but not from the RV apex, resulted in the progression of diastolic dysfunction in patients with a normal LVEF, confirmed by 2 independent imaging techniques, radionuclide ventriculography and echocardiography [38]. Therefore, it is still unclear as to how different pacing sites within the RV compare with regards to their effect on LV diastolic function. Further larger clinical studies are required to elucidate this. The effects of RVA pacing in patients with preserved LV function is also a very important area of RV pacing. The Protect-Pace study explored the effect of RV pacing lead site on LV function in patients with a high-grade AV block and preserved LV function. This study included patients with only preserved LV function requiring a high percentage of ventricular pacing, and showed that in these subjects, RV high septal pacing does not provide a protective effect on LV function over RVA pacing in the first 2 years. So, despite the fact that the follow-up period was only of 2 years duration, no change in outcome was observed [39]. Kiehl *et al.* demonstrated in their study that PICM is not uncommon in patients receiving a permanent pacemaker for complete heart block with preserved LVEF and is strongly associated with a RV pacing burden of more than 20%. Out of the 823 patients in this study, 12.3% developed PICM over the mean follow-up of 4.3 ± 3.9 years, with post-permanent pacemaker LVEF being $33.7\% \pm 7.4\%$ in patients with PICM *vs.* $57.6\% \pm 6.1\%$ in patients without PICM ($p < 0.001$). In addition, in patients with poor clinical evidence of PICM but with an echocardiographic demonstration of a small reduction of LVEF post pacemaker implantation, the latter finding is clinically important because these patients are still at risk of developing clinically-evident PICM in the long run [40]. However, it is important to emphasize that the study by Kiehl *et al.* was a retrospective and non-randomized study involving a highly selective group of patients as the majority of patients were not eligible for inclusion in the study, whereas the Protect-Pace study by Kaye *et al.* was a randomized and strictly controlled study, giving the latter study higher statistical power over the former. On the other hand, not everyone paced from

the RV apex develops PICM. With current available statistical data reporting the prevalence of PICM to be 9% 1 year after conventional pacemaker implantation, Dreger *et al.* prospectively studied the development of PICM in patients who were RVA-paced for a period of over 15 years, and found that considering the very long duration of RV stimulation in their study population (24.6 ± 6.6 years), the prevalence of PICMP was remarkably low [41]. Furthermore, Kaye *et al.* showed in their study that the prevalence of PICM can range from as low as 5.9%, to as high as 39.0%, depending on the currently accepted PICM clinical definitions, reinforcing the concept that not all RVA paced patients will go on to develop clinically-evident PICM [42]. A multicenter retrospective analysis by Kim *et al.* also demonstrated that in patients with complete AV block with pacing-dependent rhythm, the pQRS duration is a major determinant of the occurrence of PICM, regardless of the pacing site in the RV [43]. On the other hand, Khurshid *et al.* retrospectively studied 1750 consecutive patients undergoing pacemaker implantation from 2003 to 2012, and found that a longer-paced QRS duration of ≥150 milliseconds was 95% sensitive for PICM, and was therefore associated with an increased prevalence of RV PICM [44]. In summary, the baseline LV function and burden of ventricular pacing are both important in the development of PICM. Long-term RVA pacing is associated with electrical and mechanical dyssynchrony and ultimately the development of PICM in a subset of patients. Patients with a high degree of pacing burden and reduced LV function prior to pacemaker implantation are at the greatest risk for developing PICM. CRT has an established role in the treatment of patients with LV systolic heart failure and intraventricular delay and can be used to successfully treat PICM [45].

5. MINIMIZING THE DELETERIOUS EFFECTS OF RV APICAL PACING

5.1. RVNA Pacing *Versus* RVA Pacing

Up until now, the His bundle and para Hisian tissues, the midseptum, the low interventricular septum, the RVOT, and in particular, the septal portion of the RVOT constituted the alternative sites for RV pacing. The most studied of these selective sites thus far has been the RVOT septum [46], however there are increasing number of studies being conducted on HBP which will be covered separately in this review. True RV septal pacing has until recently been a difficult technique to achieve due to technical issues faced with lead placement as a result of lack of suitable lead technology, as well as difficulties with the non-standard nomenclature and with the consistent and accurate placement of the RV lead in the chosen position. Successful development of tools to reliably direct the RV active fixation lead onto the true RV septum has been achieved through a more succint understanding of the relationship between the anatomy of the RV chamber, appearances on fluoroscopy, and electrocardiographic patterns. However, it is worth mentioning that septal pacing has proven difficult even with newer stylet designs which might explain why the trials comparing apical to non-apical pacing were discordant. In their study on the use of imaging to precisely locate the RV pacing led position using CT, MRI and echocardiography, Moore *et al.* [47] found that

subsequent imaging following lead implantation showed that leads intended for the septum during implant were not confirmed as such with the imaging modality being used, and significant heterogeneity was apparent between different imaging methods. This shows that even with newer stylet designs and more advanced lead technology, optimal lead placement results with regards to septal pacing is still a major challenge. On the other hand, one challenge that still remains is the reluctant change in the mindset of pacing clinicians to switch to RV septal pacing by moving away from conventional RVA pacing, despite the availability and reliability of suitable RV leads. A potential explanation for this could be because achieving a true septal position is quite unreliable and the data comparing RV septal to apical pacing has so far proven to be conflicting.

The first Randomised Controlled Trial (RCT) by Barin *et al.* comparing RVA to RVOT pacing, showed the latter to be more feasible, with the sensing and pacing parameters at the RVOT being indistinguishable from those at the RV apex [48]. RCTs assessing alternative RV pacing sites to achieve a more physiological pacing pattern thus minimizing the deterioration of LV function, have been conducted since then. Most of the RCTs with medium to long-term follow-up used LVEF measurement as a marker of cardiovascular mortality and morbidity. They were however inconclusive due to their small sample sizes. The study conducted by Vancura *et al.* is the only one that has so far assessed the optimal RV pacing site using invasive measurement of LV systolic and diastolic function. The authors of this study demonstrated that optimal LV mechanical outcome resulted from RV septal pacing in the non-apical, mid-to-superior segments of the interventricular septum. It was also shown that pacing lower down the RV free wall and at inferior segments of the septum resulted in the worst hemodynamic response. However, one major limitation of this study was that only AF patients were enrolled. The results of this study might therefore apply only for RV pacing in patients with AF [49].

5.2. BiV *Versus* RV Pacing

Clinical studies have shown that RV pacing can produce worse outcomes compared with low-rate ventricular pacing in patients with pacemakers and ICDs having intact AV conduction [50]. Strategies minimizing ventricular pacing yet providing ventricular rate support when needed are now widely in practice for such patients [51]. However, patients with AV block may require pacing all or most of the time. The BLOCK-HF study by Curtis *et al.* [52] demonstrated that clinical outcomes, quality of life, and HF status are improved with BiV pacing as opposed to RV pacing. This shows that in addition to the main trial findings which are a decrease in the composite endpoint of death, heart failure–related urgent treatment, and adverse ventricular remodeling with BiV pacing, important clinical outcomes are improved as well. Important aspects to be taken into consideration are the fact that the BLOCK-HF trial included subjects with LVEF <50% and NYHA classes I to III and this is the reason why the European Society of Cardiology (ESC) clinical guidelines recommend CRT for patients with a pacemaker indication and LVEF <50%, if ventricular pacing is estimated to be frequent. Another study by Leclerq *et al.* demonstrated similar results by showing that the upgrade from

RVA pacing to CRT may result in a significant improvement in exercise capacity and NYHA functional class [53]. Several other trials have also highlighted the positive outcomes of the upgrade from RVA pacing to CRT. Reverse remodeling of the LV following upgrade from RVA pacing to CRT has been clearly shown in several studies [54, 55]. Furthermore, the severity of mitral regurgitation, LV hemodynamic parameters and mechanical function are likely to get better after an upgrade to CRT [56, 57]. Additionally, chronically RV-paced subjects receiving CRT display similar short-term benefits versus patients with newly implanted CRTs [58]. Finally, as demonstrated by Lieberman *et al* in their study, RV pacing does worsen LV function in patients with and without LV dysfunction unless the RV pacing site is optimized [23].

5.3. Minimal Ventricular Pacing Methods

Currently, the mainstay of pacemaker programming strategies to avoid RV pacing consists of AV search or Managed Ventricular Pacing (MVP) mode. The latter promotes intrinsic conduction by reducing unnecessary RV pacing, providing atrial-based pacing with ventricular backup and if AV conduction is lost, the device is designed to switch to DDD mode. These algorithms enhance normal AV conduction, maintain intrinsic ventricular conduction and prevent LV dyssynchrony. The INTRINSIC RV study showed that use of the AV search hysteresis algorithm was associated with similar clinical outcomes when compared with VVIR backup pacing [59]. On the other hand, the SAVE PACE trial where 1065 patients with sinus node disease and intact AV conduction were randomized between dual-chamber conventional pacing and dual-chamber MVP, showed that the RV pacing burden was significantly reduced with MVP, compared with dual-chamber conventional pacing. After 1.7 years of mean follow-up, the development of persistent AF was markedly reduced with MVP programming, with no marked difference in HF or mortality rate noted [60]. The above trials demonstrate a favorable effect of MVP algorithms, but more studies are required to appreciate the precise benefits in routine clinical practice. In addition, as demonstrated by Sweeney *et al*., DDD pacemaker implant is the standard of care for SND and normal AV conduction, due to the fact that a risk of AV block requiring upgrade at a rate of approximately 1% per year is present. Hence, minimizing ventricular pacing, instead of AAI pacemaker implant, is the current approach for these patients. The risk of AF is increased when ventricular pacing rate is >40% [29].

5.4. Reversing the Negative Outcomes of RVA Pacing

Another crucial aspect of consideration relates to the reversibility of the negative outcomes of acute and chronic RVA pacing. For example, how efficacious is switching to BiV pacing after the negative consequences of RVA pacing have been observed, or after pacemaker-induced dyssynchrony leading to cardiomyopathy has occurred. 3 important clinical studies have attempted to answer the above questions. A study conducted by Vaillant *et al*. [61] between 2007 and 2010 described a specific syndrome characterized by isolated complete LBBB that presumably led to a history of progressive LV dysfunction, and treated successfully with

CRT. The specific observations made during the study support the existence of a specific LBBB-induced cardiomyopathy that resolves with CRT implantation. The review by Guglin *et al*. [62] on the other hand successfully demonstrated the important place that CRT has in preventing and treating PICM on the basis that prolonged RVA pacing, increases LV dimensions and decreases LVEF, adverse effects which can be overcome by CRT. Furthermore, in chronically RV-paced patients with mild cardiomyopathy, switching to CRT following chronic RVA pacing has been shown to improve LV function and reverse LV remodeling [63]. These findings support the fact that in chronically RV-paced patients with mild cardiomyopathy, upgrade to CRT needs to be importantly considered.

5.5. His Bundle Pacing as Treatment for Bradycardia

Chronic RVA pacing is associated with detrimental effects, with an increased risk of HF, AF and death. Most of these adverse effects result from ventricular dyssynchrony related to perturbed ventricular depolarization. In addition, BiV pacing has limited benefits in patients with non–LBBB and severely reduced LVEF [64]. Consequently, further alternative pacing strategies are desired which most closely mimic the natural electrophysiology of the heart. Recently, permanent HBP has emerged as a true physiologic form of ventricular pacing. It has the benefit of reducing or eliminating both interventricular or intraventricular dyssynchrony because it induces ventricular contraction by exciting the intrinsic conduction system [65]. Is HBP therefore the holy grail of pacing? It is certainly largely considered to be one of the most suitable physiological alternatives to conventional RVA pacing. In addition to providing physiologic ventricular activation, HBP has interestingly been shown to correct underlying conduction abnormalities in certain patients [66]. Due to the recent emergence of this method, large prospective randomized clinical trials have not yet been completed. However, the observational clinical data available to date do already support the safety and efficacy of this novel technique. HPB is therefore emerging as a viable pacing strategy in daily clinical practice. Several investigators have already shown both feasibility and positive clinical outcomes with HBP. Proven clinical benefits include lack of pacing-induced dyssynchrony, correction of bundle branch blocks, improvement in HF symptoms and LV systolic function. With improvement in delivery tools and lead designs, HBP is likely to become a common pacing strategy across the globe in the near future [67]. In their study in 2015, Vijayaraman *et al.* explored the efficacy of HBP in patients with AV block and electrophysiological observations into the site of block in patients with infranodal AV block. It was shown from this study that permanent HBP can be successfully and safely undertaken in 84% of patients with complete AV block, and that HBP in these patients is safe and effective for at least up to 18 months [68]. The same team of investigators performed a very recent study on the long-term lead performance and clinical outcomes of permanent HBP, on the basis that RVA pacing is associated with heart failure and increased mortality such HBP could be a good physiological alternative to RVA pacing. They demonstrated that during long-term follow-up, permanent HBP led to a decrease in death or HF hospitalization rates compared to RVA pacing in patients

undergoing pacemaker implantation. However this study also showed that HBP was associated with higher rates of lead revisions and generator change, which can be a downside to this pacing strategy in clinical settings which are understaffed or with limited resources [69]. On the other hand, a 3-year clinical study by Abdelrahman *et al.* seeking to evaluate the clinical outcomes of HBP compared to RVA pacing, demonstrated that permanent HBP was feasible and safe in a large real-world population requiring permanent pacemakers. This study also showed in patients requiring permanent pacemakers, HBP was associated with a reduction in the combined endpoint of death, HF hospitalization or upgrade to BiV pacing, compared to RV pacing [70]. A systematic review and meta-analysis by Zanon *et al.* published this year aiming to systematically examine published studies of patients undergoing permanent HBP and quantify the benefits and risks of the therapy demonstrated the following results: among 26 articles of permanent HBP, the implant success rate averaged 84.8% and the LVEF improved by an average of 5.9% during follow-up. The authors however pointed out that specific reporting of their clinical outcomes of interest varied widely, which highlights the need for uniform reporting in future HBP trials [71]. Another study published this year by Ye *et al.* on the upgrade to HBP in pacing-dependent patients referred for pulse generator change, looking at feasibility and intermediate term follow-up, showed that HBP improves HF symptoms with preserved LVEF, proving that permanent HBP is feasible and safe for upgrade in patients with long term RV pacing irrespective of the LVEF [72]. This is an interesting finding as it is potentially applicable to most clinical setting throughout the world as patients are serially followed-up post pacemaker implantation, and can eventually be upgraded to HBP when they reach the time for pulse generator replacement.

5.6. His Bundle Pacing as Potential New Therapy for HF

HBP has also been shown to be a potential new frontier in HF therapy. BiV pacing has revolutionised the treatment of HF in patients with sinus rhythm and LBBB; however, LV-lead placement is not always technically possible. Furthermore, BiV pacing does not fully normalize ventricular activation and, therefore, the ventricular resynchronisation is imperfect. On the other hand, HBP activates the ventricles *via* the native His-Purkinje system, resulting in true physiological pacing, and is therefore a promising alternate site for pacing not only in bradycardia cases as shown above, but also in traditional CRT indications in instances where it can overcome LBBB. Furthermore, it may open up new indications for pacing therapy in HF, such as targeting patients with PR prolongation and a narrow QRS duration [73]. Therefore, given the fact that HBP been shown to be a safe and effective method to achieve CRT by means of recruiting the heart's physiological conduction system, it should be considered for those patients with distorted coronary sinus anatomy and unsuitable for BiV pacing, as well as patients who fail to respond to BiV pacing. HBP CRT may also help patients with the non-LBBB form of conduction delay and HF, and should be considered strongly in preventing RV PICM, especially after AV nodal ablation, given the discrete nature of the block and the low likelihood of distal block. With increased operator experience and improved lead delivery systems, HBP success rates and safety have improved and are comparable to traditional RV pacing. Battery longevity is also likely comparable to traditional BiV CRT devices and therefore, we can anticipate the use of HBP CRT to grow significantly in future [74]. The HOPE-HF trial, a multicentre, double-blind, randomized, crossover study, is currently in the process of recruiting patients. It will determine whether correcting PR prolongation in patients with HF and narrow QRS or right-BBB using haemodynamically-optimized dual chamber HBP, improves exercise capacity and symptoms, and hence will shed new light in this area of HBP [75].

5.7. LV Twist, Speckle Tracking Echocardiography and Global Longitudinal Strain

Despite the fact that the majority of RV-paced patients do not develop pacing-related HF, LV systolic dysfunction following RV pacing is often noted. The ability to predict which patients will be affected remains clinically challenging [76]. The recently-introduced 2D-speckle tracking echocardiography (STE) enables angle-independent and multidirectional assessment of LV mechanics and function that makes detection of subtle changes in ventricular mechanics possible [77]. STE thus reveals more subtle changes in LV systolic function, as compared with conventional measures such as LV ejection fraction. Accordingly, a study conducted by Delgado *et al.* assessed the acute impact of RV apical pacing on global LV function in a group of patients without structural heart disease, evaluating LV contraction synchrony and LV global longitudinal shortening and twist using 2D speckle-tracking strain imaging. In this study, speckle-tracking analysis applied to conventional 2D echocardiography was used to study the acute effects of RV apical pacing on LV mechanics. The study found that RV apical pacing acutely induced a dyssynchronous LV contraction together with a decrease LV longitudinal function. In addition, the characteristic torsional deformation of the LV during systole was impaired acutely by RV apical pacing [78]. The utility of Global Longitudinal Strain (GLS) as measured by 2D-STE to identify subclinical LV dysfunction in other medical conditions has been well-documented and GLS has also been investigated as a measure of LV dysfunction following pacemaker implantation [79-81]. For example, in STE-based studies, minor dysfunction in LV and RV mechanics, importantly between septal and apical pacing, can be accurately detected by means of GLS. In their prospective study, Ahmed *et al.* hypothesized that GLS may be reduced before significant reductions in LVEF were apparent [82]. To the best of our knowledge, this is the first prospective study designed to examine the relationship between the initiation of RV pacing and serial changes in GLS and LVEF. This study showed that GLS evaluated 1month post-pacemaker implantation is highly accurate at predicting which patients will develop PICM at a later stage. GLS is therefore a new predictor of decline in LV systolic function following pacemaker insertion, which can potentially identify patients at risk of developing cardiomyopathy secondary to pacing, even before echocardiographically-measurable changes in LVEF becomes evident. While determining who develops LV dysfunction and clinically-evident PICM is an important aspect determining long-term prognosis, the reality is that

the above cutting-edge echocardiographic technologies are not yet available to many centers throughout the world and are also not fully validated yet. Taking this fact into account, it is of interest to the current pacemaker implanter to weigh up his pacing option carefully in every patient based on the latest available evidence, individualizing the pacing strategy to each patient's requirement, thereby reducing the chance for even subtle, non-clinical PICM to develop. In that regard, regular clinic follow-up with echocardiographic evaluation using available echocardiographic technology remains of paramount importance to detect even subtle changes in LV systolic and diastolic function [83].

5.8. Novel Predictor of LV Dysfunction in Patients with RV Pacing

To date, only one study explored the potential role of a septal flash (SF), defined as an early quick inward or outward movement of the interventricular septum during isovolumetric contraction and within the QRS complex, as a predictor for the development of LV dysfunction. As a marker of LV dyssynchrony in the presence of a LBBB, SF has been demonstrated to predict improved LV function and outcome when corrected with CRT. In this study, 74 subjects on conventional RV pacing therapy were studied with two-dimensional (2D) echocardiography [84]. The presence of a SF was then determined based on stepwise advanced 2D-echocardiographic views. 57 out of the 74 patients had a detectable SF, a lower LVEF and a bigger end-systolic volume. Therefore, in this study, a SF was noted in a majority of patients receiving conventional RVA pacing therapy, and its magnitude was directly proportional to a worse LV function. SF magnitude might therefore be a predictor for the development of LV dysfunction and adverse remodeling in RV-paced subjects, given the similarities observed in LBBB and PICM. However, more clinical studies are required to validate the reliability of SF to predict LV dysfunction in patients with RV pacing.

5.9. Potential Benefits of RVA Pacing

Despite the various adverse consequences of RVA pacing, this method of pacing can paradoxically have some beneficial aspects to it. The possible positive effects of RVA pacing have been mainly demonstrated in experimental models and are usually relatively acute in nature. In their 2007 study exploring whether intermittent pacing-induced dyssynchrony occurring during early reperfusion post-iatrogenic coronary occlusion in rabbits induces protective effect on the myocardium, Vanagt *et al.* [85] showed that dyssynchrony-induced post-conditioning opens new avenues for cardioprotection in the clinical environment. Similarly, a computer simulation analysis by Lumens *et al.* demonstrated that RV free wall pacing improves RV pump function in severe decompensated pulmonary arterial hypertension, and may homogenize the workload undertaken by LV and RV free walls [86]. Further benefits resulting from RVA pacing are further substantiated by a recent study which proved that RV pacing-induced transient asynchrony can potentially suppress the progression of HF, and can thus interestingly provide the CRT benefits to the HF patients with synchronous ventricu-

lar contraction but who are unfortunately not CRT candidates [87].

CONCLUSION

RVA pacing is an integral part of the treatment of bradyarrhythmias for the majority of patients requiring pacemaker implantation. However, it is frequently a pathologic substitute for intrinsic ventricular activation over the His- Purkinje system, leading to a risk of the LVEF deteriorating or AF developing after RVA pacing in a certain number of patients. The effects of RVA pacing on LV diastolic function has been poorly validated by studies done to this date and further clinical studies are needed in this area. The assessment of the optimal RV pacing site has gained strength over recent years and in experienced hands should yield very good results in the setting of single chamber RV septal pacing, although available current data regarding long-term prognosis in patients with RV septal pacing is currently still limited. On the other hand, HBP is a feasible method for delivering permanent pacing, as it offers an alternative bradycardia pacing modality to RV pacing and has the advantage that it does not cause intraventricular dyssynchrony, and can also achieve cardiac resynchronisation in patients with HF and BBB. HBP data regarding safety, chronic sensing and pacing thresholds are encouraging but data from larger registries is still awaited, and RCT data to assess the benefits of HBP for bradycardia and HF indications are not yet available. Despite the advent of lead technology, the technical aspects of RVNA pacing remains clinically challenging even in experienced hands such that in the developed world, RVA pacing is still extensively in practice and remains currently the workhorse lead position worldwide. Furthermore, the evidence regarding whether septal pacing prevents deterioration of LV function in patients with preserved baseline LV function remains controversial. On the other hand, CRT should be considered as the first line pacing method should baseline LV function be impaired prior to pacemaker implantation, followed by RVNA pacing as second-line therapy. Further research is still required to determine which of the different modalities of ventricular pacing will best improve outcomes in patients requiring permanent pacing, this depending invariably on ongoing clinical expertise, burden of pacing required by the individual patient, baseline LV function prior to pacing, and further technological advancements with regards to lead technology, design and pacemaker function.

AUTHOR CONTRIBUTIONS

Dr. Mohammad Reeaze Khurwolah is the first and main author of this mini-review article, and is the author who wrote the full article.

Associate Professor Jing Yao critically revised the article with regards to format, structure and content, and ensured that the writing of the article was up to international standards.

Professor Xiang-Qing Kong is the principal supervising author (corresponding author) of this review article, and ensured that this article is comprehensive and relevant and meets international standard requirements.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1]   Brignole M, Auricchio A, Baron-Esquivias G, *et al.* 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J 2013; 34: 2281-329.

[2]   Sweeney MO, Prinzen FW. A new paradigm for physiologic ventricular pacing. J Am Coll Cardiol 2006; 47: 282-8.

[3]   Hillock RJ, Mond HG. Pacing the right ventricular outflow tract septum. Europace 2012; 14: 28-35.

[4]   Prinzen FW, Peschar M. Relation between the pacing-induced sequence of activation and left ventricular pump function in animals. Pacing Clin Electrophysiol 2002; 25: 484-98.

[5]   Varma N. Left ventricular electrical activation during right ventricular pacing in heart failure patients with LBBB: Visualization by electrocardiographic imaging and implications for cardiac resynchronization therapy. J Electrocardiol 2015; 48(1): 53-61.

[6]   Varma N. Left ventricular conduction delays induced by right ventricular apical pacing: Effect of left ventricular dysfunction and bundle branch block. J Cardiovasc Electrophysiol 2008; 19(2): 114-22.

[7]   Thambo JB, Bordachar P, Garrigue S, *et al.* Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Circulation 2004; 110: 3766-72.

[8]   Badke FR, Boinay P, Covell JW. Effects of ventricular pacing on regional left ventricular performance in the dog. Am J Physiol 1980; 238: H858-67.

[9]   Tops LF, Suffoletto MS, Bleeker GB, *et al.* Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. J Am Coll Cardiol 2007; 50(12): 1180-8.

[10]   Barold SS, Ovsyshcher IE. Pacemaker-induced mitral regurgitation. Pacing Clin Electrophysiol 2005; 28: 357-60.

[11]   Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: Experimental study using magnetic resonance imaging tagging. J Am Coll Cardiol 1999; 33: 1735-42.

[12]   Vassallo JA, Cassidy DM, Miller JM, Buxton AE, Marchlinski FE, Josephson ME. Left ventricular endocardial activation during right ventricular pacing: Effect of underlying heart disease. J Am Coll Cardiol 1986; 7: 1228-33.

[13]   Rodriguez LM, Timmermans C, Nabar A, Beatty G, Wellens HJ. Variable patterns of septal activation in patients with left bundle branch block and heart failure. J Cardiovasc Electrophysiol 2003; 14: 135-41.

[14]   Auricchio A, Fantoni C, Regoli F, *et al.* Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 2004; 109: 1133-9.

[15]   Prinzen FW, Augustijn CH, Arts T, Allessie MA, Reneman RS. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. Am J Physiol 1990; 259: H300-8.

[16]   Skalidis EI, Kochiadakis GE, Koukouraki SI, *et al.* Myocardial perfusion in patients with permanent ventricular pacing and normal coronary arteries. J Am Coll Cardiol 2001; 37: 124-9.

[17]   Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. J Am Coll Cardiol 1997; 29: 744-9.

[18]   Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clin Electrophysiol 1999; 22: 1372-7.

[19]   Van Oosterhout MF, Prinzen FW, Arts T, *et al.* Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998; 98: 588-95.

[20]   Vernooy K, Dijkman B, Cheriex EC, Prinzen FW, Crijns HJ. Ventricular remodeling during long-term right ventricular pacing following His bundle ablation. Am J Cardiol 2006; 97: 1223-7.

[21]   Maurer G, Torres MA, Corday E, Haendchen RV, Meerbaum S. Two-dimensional echocardiographic contrast assessment of pacing-induced mitral regurgitation: Relation to altered regional left ventricular function. J Am Coll Cardiol 1984; 3: 986-91.

[22]   Kass DA. An epidemic of dyssynchrony: But what does it mean? J Am Coll Cardiol 2008; 51: 12-7.

[23]   Lieberman R, Padeletti L, Schreuder J, *et al.* Ventricular pacing lead location alters systemic hemodynamics and left ventricular function in patients with and without reduced ejection fraction. J Am Coll Cardiol 2006; 48: 1634-41.

[24]   Dong SJ, Hees PS, Huang WM, *et al.* Independent effects of preload, afterload, and contractility on left ventricular torsion. Am J Physiol 1999; 277: H1053-60.

[25]   Matsuoka K, Nishino M, Kato H, *et al.* Right ventricular apical pacing impairs left ventricular twist as well as synchrony: Acute effects of right ventricular apical pacing. J Am Soc Echocardiogr 2009; 22: 914-9.

[26]   Liu WH, Chen MC, Chen YL, *et al.* Right ventricular apical pacing acutely impairs left ventricular function and induces mechanical dyssynchrony in patients with sick sinus syndrome: A real-time three-dimensional echocardiographic study. J Am Soc Echocardiogr 2008; 21(3): 224-9

[27]   Andersen HR, Nielsen JC, Thomsen PE, *et al.* Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997; 350: 1210-6.

[28]   Nielsen JC, Kristensen L, Andersen HR, *et al.* A randomized comparison of atrial and dualchamber pacing in 177 consecutive patients with sick sinus syndrome: Echocardiographic and clinical outcome: DANPACE study. J Am Coll Cardiol 2003; 42: 614-23.

[29]   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: MOST trial. Circulation 2003; 107: 2932-7.

[30]   Connolly SJ, Kerr CR, Gent M, *et al.* Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000; 342: 1385-91.

[31]   Wilkoff BL, Cook JR, Epstein AE, *et al.* Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. JAMA 2002; 288: 3115-23.

[32]   Brenyo A, Goldenberg I, Barsheshet A. The downside of right ventricular apical pacing. Indian Pacing Electrophysiol J 2012; 12(3): 102-13.

[33]   Hussain MA, Furuya-Kanamori L, Kaye G, Clark J, Doi SA. The effect of right ventricular apical and non-apical pacing on the short- and long-term changes in left ventricular ejection fraction: A systematic review and meta-analysis of randomized-controlled trials. Pacing Clin Electrophysiol 2015; 38(9): 1121-36.

[34]   Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. Europace 2012; 14: 81-91.

[35]   Merchant FM, Hoskins MH, Musat DL, *et al.* incidence and time course for developing heart failure with high-burden right ventricular pacing. Circ Cardiovasc Qual Outcomes 2017; 10(6): pii: e003564.

[36]   Fang F, Zhang Q, Chan JYS, *et al.* Deleterious effect of right ventricular apical pacing on left ventricular diastolic function and the impact of pre-existing diastolic disease. Eur Heart J 2011; 32: 1891-9.

[37]   Rimbas RC, Margulescu AD, Siliste C, *et al.* Left ventricular strain analysis reveals better synchrony and diastolic function for septal versus apical right ventricular permanent pacing. MAEDICA 2014; 9(3): 232-41.

[38]   Mitov V, Perisic Z, Jolic A, *et al.* The effect of right ventricle pacemaker lead position on diastolic function in patients with preserved left ventricle ejection fraction. Hell J Nucl Med 2013; 16(3): 204-8.

[39]   Kaye GC, Linker NJ, Marwick TH, *et al*. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: Results of the Protect-Pace study. Eur Heart J 2015; 36(14): 856-62.

[40]   Kiehl EL, Makki T, Kumar R, *et al*. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. Heart Rhythm 2016; 13(12): 2272-8.

[41]   Dreger H, Maethner K, Bondke H, Baumann G, Melzer C. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace 2012; 14(2): 238-42.

[42]   Kaye G, Ng JY, Ahmed S, Valencia D, Harrop D, Ng ACT. The Prevalence of Pacing-Induced Cardiomyopathy (PICM) in patients with long term right ventricular pacing - Is it a matter of definition? Heart Lung Circ 2018 Jun 27. pii: S1443-9506(18)30726-1. doi: 10.1016/j.hlc.2018.05.196.

[43]   Kim JH, Kang KW, Chin JY, Kim TS, Park JH, Choi YJ. Major determinant of the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: A multicentre, retrospective analysis over a 15-Year period in South Korea. BMJ Open 2018; 8(2): e019048.

[44]   Khurshid S, Liang JJ, Owens A, *et al*. Longer paced QRS duration is associated with increased prevalence of right ventricularpacing-induced cardiomyopathy. J Cardiovasc Electrophysiol 2016; 27(10): 1174-9.

[45]   Foley PWX, Leyva F, Frenneaux MP. What is treatment success in cardiac resynchronization therapy? Europace 2009; 11(Suppl 5): v58-65.

[46]   Hillock RJ, Mond HG. Pacing the right ventricular outflow tract septum: time to embrace the future. Europace 2012; 14: 28-35.

[47]   Moore P, Coucher J, Ngai S, *et al*. Imaging and right ventricular pacing lead position: A comparison of CT, MRI, and echocardiography. Pacing Clin Electrophysiol 2016; 39(4): 382-92.

[48]   Barin ES, Jones SM, Ward DE, *et al*. The right ventricular outflow tract as an alternative permanent pacing site: long-term follow-up. Pacing Clin Electrophysiol 1991; 14: 3-6.

[49]   Vancura V, Wichterle D, Melenovsky V, *et al*. Assessment of optimal right ventricular pacing site using invasive measurement of left ventricular systolic and diastolic function. Europace 2013; 15: 1482-90.

[50]   Lamas GA, Lee KL, Sweeney MO, *et al*. Ventricular pacing or dual-chamber pacing for sinusnode dysfunction. N Engl J Med 2002; 346: 1854-62.

[51]   Gillis AM, Purerfellner H, Israel CW, *et al*. Reducing unnecessary right ventricular pacing with the managed ventricular pacing mode in patients with sinus node disease and AV block. Pacing Clin Electrophysiol 2006; 29: 697-705.

[52]   Curtis AB, Worley SJ, Chung ES, *et al*. Improvement in clinical outcomes with biventricular versus right ventricular pacing. The BLOCK HF study. J Am Coll Cardiol 2016; 67: 2148-57.

[53]   Leclercq C, Cazeau S, Lellouche D, *et al*. Upgrading from single chamber right ventricular to biventricular pacing in permanently paced patients with worsening heart failure: The RD-CHF study. Pacing Clin Electrophysiol 2007; 30(Suppl 1): S23-30.

[54]   Leon AR, Greenberg JM, Kanuru N, *et al*. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 2002; 39: 1258-63.

[55]   Valls-Bertault V, Fatemi M, Gilard M, *et al*. Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for chronic atrial fibrillation. Europace 2004; 6: 438-43.

[56]   Eldadah ZA, Rosen B, Hay I, *et al*. The benefit of upgrading chronically right ventricle-paced heart failure patients to resynchronization therapy demonstrated by strain rate imaging. Heart Rhythm 2006; 3: 435-42.

[57]   Marai I, Gurevitz O, Carasso S, *et al*. Improvement of congestive heart failure by upgrading of conventional to resynchronization pacemakers. Pacing Clin Electrophysiol 2006; 29: 880-4.

[58]   Lipar L, Srivathsan K, Scott LR. Short-term outcome of cardiac resynchronization therapy - a comparison between newly implanted and chronically right ventricle-paced patients. Int J Cardiol 2016; 219: 195-9.

[59]   Olshansky B, Day JD, Moore S, *et al*. Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverterdefibrillator? Results of the INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AVSH in ICDs) study. Circulation 2007; 115: 9-16.

[60]   Sweeney MO, Bank AJ, Nsah E, *et al*. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med 2007; 357: 1000-8.

[61]   Vaillant C, Martins RP, Donal E, *et al*. Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. J Am Coll Cardiol 2013; 61(10): 1089-95.

[62]   Guglin M, Barold SS. The role of biventricular pacing in the prevention and therapy of pacemaker-induced cardiomyopathy. Ann Noninvasive Electrocardiol 2015; 20(3): 224-39.

[63]   Van Geldorp IE, Vernooy K, Delhaas T, *et al*. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. Europace 2010; 12(2): 223-9.

[64]   Ezzeddine FM, Dandamudi G. His bundle pacing: Is it ready for prime time? Card Electrophysiol Clin 2018; 10(1): 87-98.

[65]   Ricciardi G, Checchi L. Permanent his bundle pacing: A physiological alternative to conventional right ventricular pacing or just a futile artifice? Int J Cardiol 2018; 260: 107-8.

[66]   Ellenbogen KA, Padala SK. His bundle pacing: The holy grail of pacing? J Am Coll Cardiol 2018; 71(20): 2331-4.

[67]   Payne J, Garlitski AC, Weinstock J, Homoud M, Madias C, Estes NAM. His bundle pacing. J Interv Card Electrophysiol 2018; 52(3): 323-34.

[68]   Vijayaraman P, Naperkowski A, Ellenbogen KA, Dandamudi G. His bundle pacing in AV block. JACC Clin Electrophysiol 2015; 1(6): 571-81.

[69]   Vijayaraman P, Naperkowski A, Subzposh FA, *et al*. Permanent His-bundle pacing: Long-term lead performance and clinical outcomes. Heart Rhythm 2018; 15(5): 696-702.

[70]   Abdelrahman M, Subzposh FA, Beer D, *et al*. Clinical outcomes of his bundle pacing compared to right ventricular pacing. J Am Coll Cardiol 2018; 71(20): 2319-30.

[71]   Zanon F, Ellenbogen KA, Dandamudi G, *et al*. Permanent His-bundle pacing: A systematic literature review and meta-analysis. Europace 2018; 20(11): 1819-26.

[72]   Ye Y, Zhang Z, Sheng X, *et al*. Upgrade to his bundle pacing in pacing-dependent patients referred for pulse generator change: Feasibility and intermediate term follow up. Int J Cardiol 2018; 260: 88-92.

[73]   Ali N, Keene D, Arnold A, Shun-Shin M, Whinnett ZI, Afzal Sohaib SM. His bundle pacing: A new frontier in the treatment of heart failure. Arrhythm Electrophysiol Rev 2018; 7(2): 103-10.

[74]   Huang WA, Wassie MA, Ajijola OA. Permanent his bundle pacing for cardiac resynchronization. Curr Treat Options Cardiovasc Med 2018; 20(3): 23.

[75]   Keene D, Arnold A, Shun-Shin MJ, *et al*. Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial. ESC Heart Fail 2018; 5(5): 965-76.

[76]   Thackray SD, Witte KK, Nikitin NP, *et al*. The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. Eur Heart J 2003; 24: 1143-52.

[77]   Dreger H, Maethner K, Bondke H, *et al*. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. Europace 2012; 14: 238-42.

[78]   Delgado V, Tops LF, Trines SA, *et al*. Acute effects of right ventricular apical pacing on left ventricular synchrony and mechanics. Circ Arrhythm Electrophysiol 2009; 2(2): 135-45.

[79]   Perk G, Tunick PA, Kronzon I. Non-Doppler two-dimensional strain imaging by echocardiography–from technical considerations to clinical applications. J Am Soc Echocardiogr 2007; 20: 234-43.

[80]   Meris A, Faletra F, Conca C, *et al*. Timing and magnitude of regional right ventricular function: A speckle tracking derived strain study of normal subjects and patients with right ventricular dysfunction. J Am Soc Echocardiogr 2010; 23: 823-31.

[81]   Miller D, Farah MG, Liner A, *et al*. The relation between quantitative right ventricular ejection fraction and indices of tricuspid annular motion and myocardial performance. J Am Soc Echocardiogr 2004; 17: 443-7.

[82]   Ahmed FZ, Motwani M, Cunnington C, *et al*. One-month global longitudinal strain identifies patients who will develop pacing-induced left ventricular dysfunction over time: The Pacing and Ventricular Dysfunction (PAVD) Study. PLoS One 2017; 12(1): e0162072.

[83]   Kaye G. Pacing site in pacemaker dependency: Is right ventricular septal lead position the answer? Expert Rev Cardiovasc Ther 2014; 12(12): 1407-17.

[84]   Sarvari SI, Sitges M, Sanz M, *et al*. Left ventricular dysfunction is related to the presence and extent of a septal flash in patients with right ventricular pacing. Europace 2017; 2: 289-96.

[85]   Vanagt WY, Cornelussen RN, Baynham TC, *et al*. Pacing-induced dyssynchrony during early reperfusion reduces infarct size. J Am Coll Cardiol 2007; 49(17): 1813-9.

[86]   Lumens J, Arts T, Broers B, *et al*. Right ventricular free wall pacing improves cardiac pump function in severe pulmonary arterial hypertension: A computer simulation analysis. Am J Physiol Heart Circ Physiol 2009; 297(6): H2196-205.

[87]   Kirk JA, Chakir K, Lee KH. Pacemaker-induced transient asynchrony suppresses heart failure progression. Sci Transl Med 2015; 7(319): 319ra207.