Biventricular Pacing in Normal Hearts

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For more than half a century, pacemakers have proven to be one of the most successful medical interventions. In an effort to approximate normal cardiac physiology, pacemakers have evolved from simple to highly sophisticated devices. There is a growing demand, not only to improve overall mortality and safety in patients with existing devices, but also to improve patient quality of life. With growing evidence of left ventricular dysfunction and desychronization due to prolonged right ventricle apex (RVA) pacing, alternative ways to avoid excessive RVA pacing have been devised. In the pursuit of providing safe long-term pacing, biventricular pacing is emerging as an attractive option.

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KEY WORDS

Atrio-biventricular pacing • Pacing • Cardiac • Biventricular pacing

More than half a century has passed since the first documented use of a pacemaker.[1,2] Pacemakers have been among the most successful medical interventions, not only saving lives but also improving quality of life in patients with symptomatic bradyarrhythmias. Pacemakers have evolved from simple to highly sophisticated devices as scientists have pursued the goal of better approximating the normal cardiac physiology. With an increasing patient population living with implantable pacemakers, roughly 200,000 implanted annually in the United States alone, there is a growing demand not only to improve the safety of existing devices, but also to improve patient quality of life

(QoL).[3] Since the advent of pacemakers, the right ventricular apex (RVA) has been the site of choice for lead placement due to easy implantation technique, good sensing, and long-term stability of pacing leads. Even though deleterious effects of RVA pacing on left ventricular (LV) function including LV desynchronization, LV remodeling, and LV dysfunction/failure, have been described as early as 1925,[4] they have not garnered attention until recently. With growing evidence of LV dysfunction and desynchronization due to RVA pacing,[5-12] alternative methods to avoid excessive RVA pacing have been devised to circumvent these side effects. These different modalities include suitable pacing modes with algorithms to avoid unnecessary RVA pacing (especially for patients with intact atrioventricular [AV] conduction),[13,14] utilization of alternative and physiological pacing sites such as RV outflow tract (RVOT)/septum pacing, and His/paraHisian pacing.[15,16] To achieve similar goals, biventricular pacing promises to be an attractive mode of pacing in patients with normal hearts.

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Need for Alternate Pacing Modes

Since the advent of pacing there have been multiple randomized studies to demonstrate the superiority of one pacing mode over another with regard to mortality or morbidity (Tables 1-3).[17-20] A Danish trial comparing right atrial pacing with RVA pacing observed reduction in atrial fibrillation, stroke, and death in patients with right atrial pacing only.[21] A pilot study, the Danish Multicenter Randomised Study on AAI Versus DDD Pacing in Sick Sinus Syndrome (DANPACE), compared atrial pacing with dual-chamber pacing; it showed the lowest incidence of atrial fibrillation and thromboembolic events in the atrial pacing group.[22] Right atrial pacing maintains physiological ventricular activation in patients with intact AV conduction with no bundle branch blocks. In contrast, RV pacing initiates an asynchronous sequence of electrical activation leading to early activation of the septum and late activation of the inferolateral area of the left ventricle, resulting in asynchronous contraction of the ventricular myocardium. This asynchrony leads to a heterogeneous strain pattern and inefficient contraction, leading to poor cardiac performance.[6] In clinical practice, atrial-based pacing is less favored because of the lingering fear of developing complete heart block and death. In patients who have documented AV nodal disease, which is a major indication for pacing, there is no role for atrial pacing.

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TABLE 1

Atrial- Versus Ventricular-Based Pacing

Study	Follow-Up (y)	Indication	Pacing Mode	Atrial Fibrillation (RR)	Thromboembolic Events (RR)	Mortality	Comments
Andersen HR et al.[21]	5.5	SND	AAI, VVI	0.54; 95% CI, 0.33-0.89; $P = .012$	0.47; 95% CI, 0. 24-0.92; $P = .023$	0.47; 95% CI, 0.27-0.82; $P = .0065$	First randomized trial to show decrease in AF, CHF, and mortality with atrial compared with ventricular pacing

AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence interval; RR, risk reduction; SND, sinus node dysfunction.

TABLE 2

Atrial-Based Pacing Versus Dual-Chamber Pacing

Study	Follow-Up (y)	Indication	Pacing Mode	Atrial Fibrillation (%)	Thromboembolic Events (%)	Mean Ventricular Pacing (%)	Echocardiographic Parameters
Kristensen L et al.[22] (DANPACE Pilot)	2.9	SSS	AAIR; DDDR-s; DDDR-l	7.4 vs 23.3 vs 17.5	5.6 vs 11.7 vs 6.3	0 vs 90 vs 17	
Kristensen L et al.[73] (DANPACE)	2.9	SSS	AAIR; DDDR-s; DDDR-l	—	—	—	In both DDDR groups left atrial diameter increased significantly ($P < .05$)

DANPACE, Danish Multicenter Randomised Study on AAI Versus DDD Pacing in Sick Sinus Syndrome; SSS, sick sinus syndrome.

TABLE 3

Dual-Chamber Pacing Versus Right Ventricular Pacing

Study	Follow-Up (Mo)	Patients (N)	Pacing Mode	Primary Endpoints	Mortality	Comments
Lamas GA et al.[19] (PASE)	18	407	DDDR, VVIR	QoL	No significant difference	No significant difference in death, AF, QoL, or stroke between two groups, but AF was less in DDDR group with SSS, not those with AV block
Connolly SJ et al.[17] (CTOPP)	36	2568	VVIR, DDDR, AAIR	Death, stroke	No significant difference	No significant difference in death, CHF, QoL, or stroke between two groups, but AF was less in DDDR group with SSS, not those with AV block
Lamas GA et al.[18] (MOST)	33	2010	VVIR, DDDR	Death, stroke	No significant difference	DDD was associated with improved QoL measures; heart failure scores were better and less AF in SSS group compared with VP
Toff WD et al.[20] (UKPACE)	56	2021	VVI, VVIR, DDDR	Death	No significant difference	Did not show any benefit of DDD over VP, especially in patients with AV block

AF, atrial fibrillation; AV, atrioventricular; CHF, congestive heart failure; CTOPP, Canadian Trial of Physiologic Pacing; MOST, Mode Selection Trial in Sinus-Node Dysfunction; PASE, Pacemaker Selection in the Elderly; QoL, quality of life; SSS, sick sinus syndrome; UKPACE, United Kingdom Pacing and Cardiovascular Events; VP, ventricular pacing.

Following the Danish study[21] that compared atrial-based pacing with ventricular pacing, there were multiple major trials such as the Pacemaker Selection in the Elderly (PASE),[19] Mode Selection Trial in Sinus-Node Dysfunction (MOST),[18] the Canadian Trial of Physiologic Pacing (CTOPP),[17] and United Kingdom Pacing and Cardiovascular Events (UKPACE),[20] that compared dual-chamber pacing with RV pacing. Some of these trials suggested the superiority of dual-chamber pacing in terms of incidence of pacemaker syndrome and QoL measures,[18,19] and others demonstrated reduced incidence of atrial fibrillation with dual-chamber pacing[17,19]; however, none showed any significant clinical or survival benefit of dual-chamber pacing over RV pacing.[17,19,20] A recent meta-analysis confirmed no survival advantage with dual-chamber pacing over RV pacing, but revealed a statistically significant beneficial effect regarding the prevention of atrial fibrillation (odds ratio 0.79; 95% confidence interval [CI], 0.68-0.93).[23] These results were surprising due to the fact that dual-chamber pacing did not show any mortality benefit over RV pacing. Therefore, a new belief arose from these observations—that long-term RV pacing may have detrimental effects on the left ventricle despite producing AV synchrony.

Wiggers[4] demonstrated detrimental effects of RVA pacing on LV hemodynamics as early 1925, and his observations have been reiterated in many recent observational studies, animal studies, and human trials.[6,11,24,25] The initial breakthrough in supporting Wiggers' data came from the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial,[11] which documented a higher incidence of heart failure hospitalizations or death in patients who had received dual-chamber pacing. These findings were attributed to an increase in RV pacing in the dual-chamber group.

Sweeney and colleagues,[6] in a randomized study, observed higher risk of heart failure hospitalization in the DDDR-paced patients; they attributed their findings to ventricular desynchronization. Cumulative percentage of ventricular pacing was higher in the DDDR patient population, and was correlated as a strong predictor of heart failure hospitalization.[6] When patients with complete congenital AV block and dual-chamber pacing were compared with healthy control subjects, they were found to have a higher intra-LV asynchrony with detrimental left ventricle remodeling, dilatation, asymmetrical hypertrophy, and low cardiac output with decreased exercise capacity in long-term follow-up.[8] This observation was confirmed by multiple studies.[7,9,10,12,26]

Predictors of RVA Pacing Outcomes

Although abnormal LV function, desynchrony, and remolding are observed in two-thirds of patients after RV pacing,[7,9] only 3% to 10% developed heart failure.[18,27] This finding suggests the incidence of heart failure depends on patient-specific and pacing-related factors that include baseline atrial rhythm, intrinsic AV nodal and ventricular conduction, LV ejection fraction (LVEF), baseline heart failure, and/or coronary artery disease.[27] Patients with low LVEF and coronary artery disease at baseline showed a higher incidence of new-onset or worsening heart failure with RV pacing.[11,28] The relative risk of heart failure increased in patients with a higher percentage of RVA pacing, independent of the mode of pacing.[6,27] QRS duration of paced beats is also identified as an independent predictor of new-onset heart failure after RVA pacing.[12] A prolonged QRS may itself represent a severe LV desynchrony during pacing and/or may contribute to underlying conduction defects, which together may contribute to a higher incidence of heart failure.[12] Recent studies have shown higher incidences (26%) of heart failure in patients with extended periods (7-8 y) of RV pacing.[12]

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Pathophysiology of LV Dysfunction Due to Prolonged RVA Pacing

Normal conduction of electric impulse through the heart occurs rapidly, beginning in the SA node, which generates electric impulses that are conducted through the AV node to the highly specialized His-Purkinje pathway, leading to depolarization and contraction of myocardium. Conduction is rapid, 3 to 4 m/s, leading to synchronized depolarization (in 80 ms) of ventricles, which is central to optimal LV function.[29,30] In a left bundle branch block (LBBB), ventricular depolarization starts in the right ventricle, and the left ventricle is activated by right to left trans-septal conduction, causing a prolongation of LV depolarization time. A similar LV activation pattern is observed in RVA pacing. However, prior studies have suggested the presence of pacing waveforms recruiting the distal Purkinje system after exiting the right ventricle[31]; nonetheless, during RVA pacing the last myocardial region activated has consistently

been the inferior-lateral base.[32,33] Asynchronous depolarization leads to early activation of the left ventricle adjacent to the pacing site, resulting in an untimely contraction, then resulting in lower chamber pressure to produce ejection. This wastes energy, causes prestretching, and increases workload in the last activated portion of the left ventricle.[34]

The other proposed mechanisms for detrimental effects of RVA pacing include redistribution of regional myocardial mechanical work and perfusion due to changes in contraction pattern,[34-36] asymmetrical hypertrophy, ventricular remodeling with LV dilatation,[37-39] and redistribution in sympathetic innervations, which contributes to asymmetrical LV hypertrophy due to local increase in catecholamine release.[35,40,41] Furthermore, histologic changes contributing to the underlying mechanism include myofibrillary disarray, dystrophic calcification, and disorganized mitochondria.[35,42] New mitral valve regurgitation or worsening of preexisting mitral valve regurgitation has also been associated with RVA pacing.[43]

Attempts to Minimize RVA Pacing

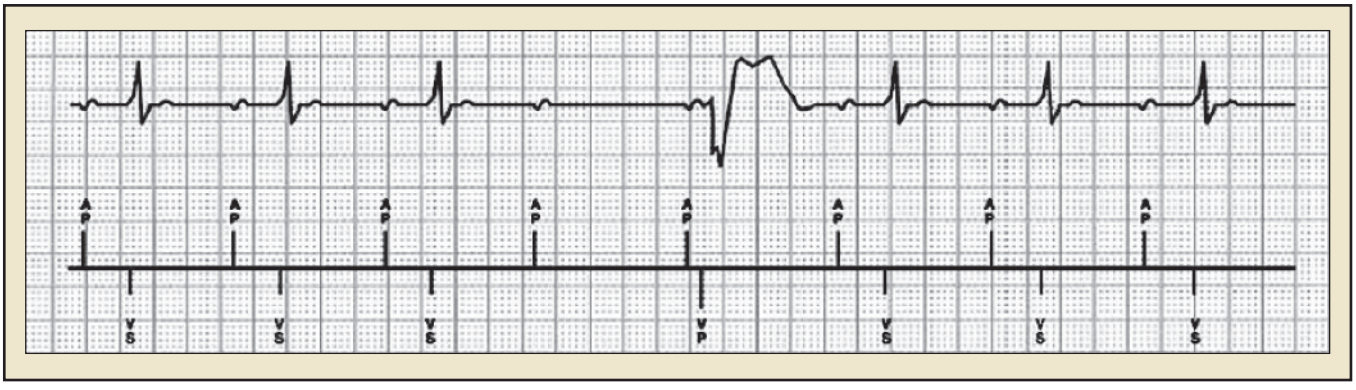
Due to the deleterious effect of long-term RVA pacing, alternative modes and pacing sites have been investigated to minimize its use. Although AAI appears promising to avoid unnecessary ventricular pacing,[21] pacing in patients with complete heart block remains a concern. The other known risks associated with AAI include future AV block, future use of antiarrhythmic medication, and slow ventricular response to atrial tachyarrhythmia.

Manual programming to prolong AV interval to promote intrinsic AV conduction has been used in minimizing ventricular pacing. However, this mode interfered with automatic mode switching during atrial tachyarrhythmia, which is required to prevent unnecessary high-rate ventricular pacing.[44] Additionally, a higher percentage of RV pacing was observed in fixed long AV interval due to dynamic variation of AV nodal conduction.[45]

Some other pacing modes have used an AV hysteresis algorithm, in which AV delay is transiently increased to search for intrinsic conduction[13] and managed ventricular pacing, in which mode switch between AAI to DDD occurs when the device detects AV block to limit RV pacing (Figure 1).[14] Recent studies show that these modes can decrease RV pacing to 10%.[13,46] Although minimal pacing modes have demonstrated a reduction in RVA pacing in patients with low- to intermittent-degree AV conduction diseases, they cannot be used in patients with high-degree AV block and complete heart block. Thus, the need for alternative pacing sites arises to avoid detrimental effects on the left ventricle and maintain efficient cardiac performance in paced hearts. The alternative sites studied and utilized include RVOT/septum and His/paraHisian pacing.

RVOT was the first reported site of pacing[2] but was not in practice until the advent of the active fixation endocardial lead system.[47] Recent evidence confirms RVOT pacing to be stable, feasible, and efficacious, with a low risk of RV perforation, diaphragmatic stimulation, easy lead extraction, and acceptable pacing and sensing thresholds.[48,49] Current data have shown a discrepancy in potential benefits of RVOT over RVA pacing.[10,50-54] Multiple factors contributing to these conflicting results include an imprecise definition and location of the pacing site in the ventricular septum, short duration of follow-up, and small, nonrandomized studies. The studies that defined pacing site precisely, with a duration of follow-up $>$ 6 months, showed RVOT preserved LV function.[10,52,54] However, a recent large cohort study with $>$ 18-month follow-up did not confirm these results.[48]

Figure 1. Managed ventricular pacing and detection of complete heart block and initiation of dual chamber pacing.



His/paraHisian pacing in canines was achieved for the first time in 1967 through an open chest epimyocardial approach.[55] His-bundle pacing appears promising as the closest pacing site that approximates natural physiology by depolarizing ventricles through the intrinsic His-Purkinje system, maintaining synchrony, and avoiding the deleterious effects seen with RVA pacing. Multiple studies have proven His-bundle pacing to be superior to RV pacing in improving mitral regurgitation and LV dyssynchrony.[15,16] Other studies have documented improvement in New York Heart Association (NYHA) functional class and LVEF as well as improvement in LV dimensions and cardiothoracic ratios.[56-58] Theoretically, paraHisian pacing can be achieved only in patients with intact and functional distal conduction systems, which is usually unpredictable in reliability, given the slow progression of conduction disturbances distal to the pacing site. The other important challenges associated with His-bundle pacing are high pacing thresholds and unreliable sensing. Major improvements in equipment technology and more accuracy in techniques may resolve some of these issues.

Biventricular Pacing

To date, there is clear evidence that RV pacing is not absolutely safe in patients who need long-term pacing. Whether biventricular pacing is a preferable and safer alternative for patients with normal heart function who require permanent pacing can be justified based on animal studies and a few randomized human trials that have shown preservation of LV function and less ventricular desynchronization compared with RV sites.[24,25,59-63] Interestingly, biventricular pacing has also been observed to resynchronize ventricular contraction in HF patients with LBBB, leading not only to reversal of LV remodeling over time but also increased functional capacity, resulting in an improvement in mortality and QoL, thus reversing the desynchronization induced by RVA pacing.[60,62,64]

Wyman and colleagues[25] studied the temporal synchrony and spatiotemporal distribution of LV contraction in eight dogs during right atrial, RVA, and biventricular pacing using tagged magnetic resonance imaging; the study concluded biventricular pacing improved the temporal synchrony of contraction with an even greater improvement in the spatiotemporal synchrony of contraction over RVA pacing alone. Biventricular pacing reduced the spatiotemporal asynchrony by eliminating the prestretch in the late-activated region opposite the pacing site. The authors observed the rate of rise of LV pressure (dP/dt_{max}), which represents a systolic function index, was 37% higher during biventricular pacing than RVA pacing.[25] Improved LV performance was observed in the acute canine model of AV block with epicardial biventricular pacing compared with chronic single-site RV pacing. In this study, LV impedance catheters were used to assess cardiodynamics using instantaneous LV pressure-volume relations.[24] Cojoc and colleagues[60] investigated the same in piglets using tissue Doppler and impedance catheters, and found LV performance improved with biventricular pacing as compared with single-site pacing from the RVA. The tissue Doppler confirmed reversal of desynchrony due to RVA pacing back to normal with biventricular pacing.[60]

Following these animal studies, similar studies were conducted in humans producing similar results.[59,61,62] Simantirakis and associates[61] investigated LV mechanics under LV-based pacing and RVA pacing in 12 patients, half of whom had normal systolic function. The investigators used conductance catheters and analyzed LV pressure-volume loops during routine coronary angiography, revealing the superiority of LV-based pacing over RVA pacing in terms of contractile function and LV filling. In addition, LV systolic function indexes, including end-systolic pressure and volume, cardiac index, stroke work, preload recruitable stroke work, maximal rate of rise of LV pressure (dP/dt_{max}), LVEF, and end-systolic elasticity showed improvement in LV-based pacing.[61] A study of permanent RV pacing and its effect on LV desynchrony using Speckle-tracking strain revealed permanent RV pacing induced LV desynchrony in 57% of patients, with subsequent deterioration of LV systolic function and NYHA functional class. However, upgrading the conventional pacemaker to a biventricular pacemaker resulted in partial reversal of the detrimental effects of RV pacing, including partial reversal of dyssynchrony, improvement in LVEF, and improvement in NYHA functional class.[62]

The first small, randomized trial comparing conventional DDDR pacing with biventricular pacing observed LVEF decreased significantly at 12-month follow-up, whereas LVEF remained unchanged in the biventricular group after 12 months. Dyssynchrony was more prominent in the DDDR group than in the biventricular group at baseline and at 12-month follow-up. N-terminal precursor of brain natriuretic peptide (NT pro-BNP) was unchanged in the DDDR group during follow-up but decreased significantly in the biventricular group.[59] Recently, the Pacing to Avoid Cardiac Enlargement (PACE) trial, a double-blind, multicenter, prospective,

randomized trial, compared RVA and biventricular pacing in normal LVEF and symptomatic bradycardia. Patients were followed for 12 months. The investigators observed mean LVEF was significantly lower in the right ventricular pacing group than in the biventricular pacing group, whereas the LV end-systolic volume was significantly higher in the right ventricular pacing group than in the biventricular pacing group, which was attributed to adverse remodeling of left ventricle secondary to RVA pacing.[63] More recently, follow-up at 24 months from the same patient cohort reinforced the previously observed findings.[64] It is noteworthy that patients enrolled in this trial had sinus-node dysfunction and were exposed to potentially detrimental effects of right ventricular pacing that could have been avoided by methods mentioned above. Enrollment criteria should have been limited to patients with high-grade AV block.

Upgrading RV pacing to biventricular pacing in patients with chronic RV pacing with mild LV dysfunction and remodeling has shown improvement in LV function and reversal of LV remodeling.[65] Multiple studies have demonstrated that biventricular pacing is superior to conventional RV pacing in patients with LV dysfunction who need permanent ventricular pacing support but do not meet criteria for cardiac resynchronization therapy (CRT).[66,67]

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A benefit in morbidity and mortality from biventricular pacing (CRT) is well established in chronic heart failure patients in NYHA class III or IV with LV dysfunction and prolonged QRS duration.[68,69] Biventricular pacing has been shown to reverse LV remodeling and slow disease progression in NYHA class III and IV heart failure patients.[67,68] It was then hypothesized that these findings may be extrapolated to demonstrate benefit in NYHA class I and II heart failure patients. Initial small studies showed no significant benefit of biventricular pacing on functional status or QoL but suggested reversal of LV remodeling in NYHA class I and II patients.[70,71] Recently, larger randomized trials, including the Resynchronization Reverses Remodeling In Systolic Left Ventricular Dysfunction (REVERSE)[71] and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT),[72] studied biventricular pacing in a similar patient demographic. Even though the REVERSE trial failed to reach its intended primary endpoint of heart failure clinical composite response; secondary findings suggest biventricular pacing may slow progression of heart failure in patients in NYHA class I and II via slowing of LV remodeling. The MADIT-CRT trial studied a similar but larger patient population as REVERSE, and showed that 17.2% of patients in the biventricular pacing group (CRT) and 25.3% in the implantable cardiac defibrillator (ICD) group experienced the primary endpoint of all-cause mortality or heart failure event (hazard ratio 0.66; 95% CI, 0.52-0.84; $P = .001$).[72] Mortality

MAIN POINTS

- Deleterious effects of right ventricular apex (RVA) pacing on left ventricular (LV) function include LV desynchronization, LV remodeling, and LV dysfunction/failure.
- Multiple major trials compared dual-chamber pacing with RV pacing. Some suggested the superiority of dual-chamber pacing in terms of incidence of pacemaker syndrome and quality-of-life measures, and others demonstrated reduced incidence of atrial fibrillation with dual-chamber pacing; however, none showed any significant clinical or survival benefit of dual-chamber pacing over RV pacing.
- Due to the deleterious effect of long-term RVA pacing, alternative modes and pacing sites have been investigated to minimize its use, including right ventricular outflow tract and His-bundle pacing.
- There is clear evidence that RV pacing is not absolutely safe in patients who require long-term pacing. Whether biventricular pacing is a preferable and safer alternative for patients with normal heart function can be justified based on animal studies and randomized human trials that have shown preservation of LV function and less ventricular desynchronization.

in mild heart failure (NYHA class I and II) is low; therefore, the long-term benefits of biventricular pacing in terms of mortality is difficult to demonstrate and we have to wait for another randomized trial with a large patient population to see this benefit.

Conclusions

Chronic RV pacing was proven to be detrimental on left ventricular systolic function. Clear benefits of biventricular pacing were documented in patients with severe heart failure. There is evidence that patients with preserved LV function requiring chronic RV pacing may benefit from biventricular pacing. Additional studies are warranted to evaluate survival benefits, functional improvements cost-to-benefit ratio, and incidence of procedure complications prior to making definitive recommendations. Additionally, patients with mild heart failure, NYHA class I and II, who require long-term pacing or ICD and do not fulfill the present criteria for CRT, should also be considered for biventricular pacing. ■

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