How Harmful is Conventional Right Ventricular Apical Pacing? Iatrogenic Left Bundle Branch Block: Need for Alternate Site Pacing

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ABSTRACT

The right ventricular (RV) apex has been used as the traditional pacing site since the development of transvenous pacing in 1959. Some studies suggest that pacing the RV apex may cause an “iatrogenic” left bundle branch block and remodeling of the left ventricle and is therefore harmful. In the past decade, the need for alternate site pacing became imperative and there have been a multitude of studies of the hemodynamic, electrophysiological, electrocardiographic, and clinical effects of ventricular pacing at other sites. Pacing of the left ventricle singly or with biventricular pacing has emerged as an effective and safe therapy for moderate to severe congestive heart failure in patients with prolonged QRS complexes. Studies of alternate RV sites, like the RV outflow tract, have given mixed results, and further clarification of the specific sites of the RV outflow tract is needed. Direct His-bundle pacing is an attractive alternate pacing site because of the possible hemodynamic benefits that could be obtained by a normal activation sequence, but the small size and anatomic position of the His bundle have made this approach difficult. Bifocal RV resynchronization therapies have been used as an alternative to biventricular pacing.

INTRODUCTION

Since the first report of the use of the transvenous route for pacemaker implantation in 1959 by Furman, the right ventricular (RV) apical region has represented the preferred pacing site [1]. The main reason has been the ease of implantation and the stability of passive-fixation leads in the apical trabeculae. However, apart from some specific diseases like hypertrophic cardiomyopathy, RV apical pacing often results in substantial functional, hemodynamic, electrical, and structural changes as already demonstrated in many studies. It is interesting to note that the roentgenogram from the early report of Furman shows the pacing lead position in the RV outflow tract (RVOT) [1]. As early as 1925, Carl Wiggers showed that RV apical pacing was associated with a diminished dP/dt and an asynchronous contraction pattern [2]. It is only in recent years that interest in the use of alternate pacing sites has developed.

Tse et al [3] have shown that RV apical pacing produces significant myocardial perfusion defects, apical wall-motion abnormalities (incidence increases with the duration of pacing), and worsening of global left ventricular function during long-term pacing. Several other studies confirmed the hypothesis that RV apical pacing negatively
effects systolic and diastolic function [4-7]. Permanent RV apical pacing was also shown to induce abnormal histological changes, asymmetrical hypertrophy, and thinning of the left ventricle [8,9]. The adverse effect of RV apical pacing on cardiac function was demonstrated in patients with normal6 and reduced left ventricular ejection fraction [10]. Such findings are important because they strongly suggest that RV apical pacing may promote progression of heart failure (HF) in patients with left ventricular dysfunction.

The distance of the pacing site in the RV from the His-Purkinje system causes a prolongation of the QRS complex [11] and substantial changes of the activation pattern compared with the normal physiological status [12]. In 1925, Wiggers [2] proposed that with longer distances from the artificial pacing site to the His-Purkinje system the resulting beats would be weaker. Experimental animal studies demonstrated a negative linear correlation between acute hemodynamic changes and ventricular activation time expressed as the QRS width during pacing at different pacing sites [13,14]. Based on these data, it may be expected that pacing in or near the His-Purkinje system will lead to faster and more homogenous ventricular activation with a corresponding reduction in QRS duration and a more favourable hemodynamic response.

**SPONTANEOUS LEFT BUNDLE BRANCH BLOCK (LBBB)**

Approximately 15% of all heart failure patients have an inter- or intra-ventricular conduction delay (QRS >120 ms) [15,16]. Over 30% of moderate to severe HF patients have a prolonged QRS. The prevalence of conduction defects increases with severity of HF [17-19]. Shenkman and colleagues [16] found the factors associated with prolonged QRS to include older age, male gender, Caucasian race, lower ejection fraction (EF), and higher left ventricular end diastolic diameter. About a third of patients with systolic HF show widening of the QRS complex on the surface electrocardiogram (ECG) usually in combination with left bundle branch block (LBBB).

Masoudi and colleagues [20] used retrospective medical chart data of 19,710 pts Medicare beneficiaries hospitalized for HF and in whom left ventricular systolic function was confirmed. LBBB was present in 8% of those with preserved left ventricular systolic function (diastolic HF) and in 24% of those with EF <50% (p<0.001). Aaronson [18] developed and validated a multivariable survival model for ambulatory advanced HF patients wait-listed for a heart transplant. Intraventricular conduction delay (IVCD) (QRS >120 ms) was present in 27% of the 268 patients in derivation sample, and in 53% of the 199 patients in validation sample. IVCD was identified as contributing risk factor. Other studies have shown that of the entire HF population about 15% have a wide QRS. LBBB affects prognosis in patients with HF and is also associated with increased overall mortality and higher risk of sudden death [21]. Interventricular conduction disturbances are common in HF patients, mainly as QRS >150 ms (mean 27%), while worsening of HF is associated with QRS complex widening. Increased 1-year mortality with presence of complete LBBB (QRS >140 ms) has been shown [22]. Risk remains significant even after adjusting for age, underlying cardiac disease, indicators of HF severity, and HF medications. The VEST Study [23] demonstrated that QRS duration was found to be an independent predictor of mortality. Patients with wider QRS (>200 ms) had five times greater mortality risk than those with the narrowest (<90 ms). Resting ECG is a powerful, sensitive, accessible and inexpensive marker of prognosis in patients with dilated cardiomyopathy and congestive HF. The presence of LBBB creates functional abnormalities in HF patients [25], increases isovolumic contraction, increases relaxation time, and diminishes the filling time. Atroventricular (AV) conduction disturbances are also common in HF patients, mainly as PR interval prolongation (>200 ms), in up to 60% in this population [24].

The last few years, new terms have been introduced: Ventricular dyssynchrony is defined as the effect caused by intra- and inter-ventricular conduction defects or bundle branch block. What we know about the causes of ventricular dyssynchrony [26] is that inter- or intra-ventricular conduction delays usually manifest as LBBB, regional wall motion abnormalities are associated with increased workload and stress compromising ventricular mechanics and disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency. It is estimated that approximately 20% of all HF patients may have ventricular dyssynchrony [27].

**Cardiac resynchronization** therapy (CRT) is defined as the therapeutic intent of atrial synchronized biventricular pacing for patients with HF and ventricular dyssynchrony. The aim of this therapy is to resynchronize the ventricular activation sequence, and to better coordinate atrio-ventricular (AV) timing to improve pumping efficiency. Cardiac resynchronization therapy is currently indicated for the reduction of symptoms of moderate to severe HF (New York Heart Association-NYHA functional class III or IV) in those patients who remain symptomatic despite stable, optimal medical therapy, and have a left ventricular ejection fraction (EF) ≤35% and a QRS duration ≥130 ms. An implantable cardioverter defibrillator (ICD) is also available for patients with a standard ICD indication who also meet the above listed criteria. Using atrial-synchronized biventricular pacing in combination with optimal drug therapy has been shown to significantly improve patients' symptoms.

**RIGHT VENTRICULAR APICAL PACING**

**RIGHT VENTRICULAR APICAL PACING AND IATROGENIC LBBB (IATROGENIC DYSSYCHRONY)**

Over the last few years, it became obvious that not only the
spontaneous LBBB is harmful for the patients, but the iatrogenic LBBB produced by RV apical pacing is equally deleterious. The first-order pacing goal was resolution of bradycardia. Later on, atrial leads were added to establish AV synchrony. Pacing leads were designed for easy and reliable delivery to the RV apex and right atrial appendage, where the position is considered convenient and stable after years of clinical practice. There is strong evidence that long-term RV apical pacing might promote HF [28-31] and atrial fibrillation [28,30-33] and increase morbidity and mortality [29,31]. Animal and clinical data show that RV apical pacing results in asynchronous left ventricular activation and contraction [34-36].

Long-term RV apical pacing leads to: 1) Altered left ventricular electrical and mechanical activation; 2) Altered ventricular function, that means less work produced for given left ventricular end-diastolic volume and delayed papillary muscle activation leading to valvular insufficiency; 3) Remodeling due to modified regional blood flow patterns, increased oxygen consumption without increase in blood flow (60% change in blood flow between early and later activated regions) and abnormal thickening of left ventricular wall; and 4) Cellular disarray expressed as fibrosis (away from pacing lead location), fat deposition, calcification and mitochondrial abnormalities.

The performance of the left ventricle differs when comparing sinus rhythm and RV apical pacing, the main difference being the presence of only a single break-out site on the left ventricular endocardium with apical pacing. Early work by Cassidy et al [37] showed that during sinus rhythm there are two break-out locations on left ventricular endocardium (in the inferior border of the mid-septum and the superior basal aspect of free wall), while latest activation takes place in the base of the inferior posterior wall due to muscular conduction (less Purkinje fiber density). Later on, work by Vassallo et al [38] showed that during RV apical pacing there is single break-out location on the left ventricular endocardium similar to LBBB, while latest activation is similar to the intrinsic (infero-posterior base) pattern.

The performance of the left ventricle is altered. While recent evidence has focused on altered left ventricular function with RV apical pacing in humans, earlier studies in animals suggested that pacing from the RV apex was not "optimal". Note that some of these studies precede Medline. In 1925 Wiggers [2] stated that "the initial slower rise of intra-ventricular pressure is prolonged, isometric contraction phase is lengthened, the gradient is not so steep, the pressure maximum is lower, and the duration of systole is increased." He observed a double contraction process, artificial stimuli inducing local fractionate contractions which mean slow conduction, whereas when the impulse reaches the Purkinje system the conduction is rapid. Later on in 1964, Lister [12] found greater reduction in cardiac output when pacing was performed from ventricular sites associated with longest total activation time due to muscle conduction. He also found conduction velocity differences: Purkinje= 2-4 m/s, muscle= 0.2-1 m/s. In 1971 Boerth and Cowell [39] found reduced left ventricular pressure, wall stress, and dP/dt despite normal perfusion. In 1986 Burkoff [40] stated that the more muscle mass activated by muscle conduction rather than Purkinje conduction, the weaker the beat (theory of "ineffective muscle mass"), while in 1988 Rosenqvist [41] noted increased incidence of congestive HF in ventricular paced patients.

Altered myocardial perfusion. In 1985 Heyndricksx and coworkers [4] found that the coronary blood flow was higher despite decreased cardiac output. Work by Prinzen (1990) [42] demonstrated that altered electrical activation of the left ventricle precipitates non-homogeneous left ventricular wall strain and, consequently, myocardial perfusion defects. He observed similarity in behavior of electrical activation, fiber strain and blood flow but redistribution of strain and blood flow with RV pacing (early activated regions 60% blood flow of late activated regions), while the regions of the heart activated via the Purkinje system (simultaneous activation) have greater fiber strain and blood flow. In 1997 Tse and Lau [3] showed that long-term RV apical pacing resulted in high incidence of myocardial perfusion defects that increased with the duration of pacing. These myocardial perfusion abnormalities were associated with wall motion abnormalities and impaired global left ventricular function.

Apical pacing histopathology: Altered strain patterns in the left ventricle can induce cellular and sub-cellular remodeling, as well as fibrosis and calcification. It is of note that this occurs a distance from the pacing lead location. Studies by Karpawich in 1990 [43] in pediatric canine model showed left ventricular myofibril disarray which was found after 4 months of pacing from the RV apex (90 degree misalignment of adjacent fibers (stress related??)). He also noted appearance of prominent Purkinje cells in the subendocardium, variable-sized mitochondria, and dystrophic calcification. In 1999 the same investigator [44] in pediatric patients, noted myofibril hypertrophy, intracellular vacuolation, degenerative fibrosis, and fatty deposits in the left ventricle after more than 3 years of RV apical pacing. The findings were independent of paced time, patient age, epi- or endocardial lead placement, and mode.

Human RV apical pacing studies have also been performed. Those studies have noted impaired diastolic function (Betocchi et al [45], Bedotto et al [46], Stoijnic et al [47]), reduced systolic contraction (Betocchi et al [45], Tse and Lau [3]), and altered myocardial perfusion (Tse and Lau [3]).

Recent clinical trials have drawn the same conclusion that pacing from the RV apex can lead to left ventricular dysfunction independent of pacing mode. The very important MADIT-II study, except the very useful use of ICD in post-infarction patients with low EF which the study showed, importantly also showed that among these patients there was
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Here is depicted the “Wiggers” diagram of hemodynamics and steps through the left ventricular pressure-volume (LV-PV) loop. At the beginning of the cardiac cycle, both pressure and volume in the ventricle are low at the time of mitral valve opening (MVO). During left ventricular filling, volume increases and pressure stays relatively low. Once the ventricle has depolarized and begun to develop pressure, the mitral valve closes (MVC). The ventricular pressure then increases dramatically with no change in volume as the ventricle prepares for ejection during isovolumic contraction. Eventually, left ventricular pressure exceeds arterial pressure and the aortic valve opens (AVO) and ejection proceeds. Left ventricular pressure remains high during ejection as volume decreases. As relaxation ensues, left ventricular pressure drops below aortic pressure and the aortic valve closes (AVC). Finally, isovolumic relaxation continues as the ventricle actively relaxes in preparation for the next filling cycle. The area inside...
the loop is known as “Stroke Work,” and is equal to the work performed by the left ventricle to eject the stroke volume. The width of the P-V loop is the “Stroke Volume”. Proper interpretation of the shape of the left ventricular loop can provide insights into changes in systolic and diastolic left ventricular function, preload, afterload, and synchrony of left ventricular contraction.

In figure 2, PV loop analysis from 13 patients with normal left ventricular function is shown. Data were collected [56] from 13 patients during acute atrial overdrive pacing (AAI), as well as during dual chamber pacing, with different ventricular activation sites including His, RV apex, RV free wall (RVFW), RV septum, and a single left ventricular site. All loops were collected at the same overdrive heart rate with a short AV delay (atrium to His delay –10 ms). The patient shown, had normal ejection fraction and no history of HF. Looking at the loops, the following main points are made: (1) Left ventricular function changes with pacing site as evidenced by changes in the width of the loop. Interestingly, the optimal site of pacing may vary with different patients, that is, there is no “sweet spot”; (2) In this patient, with normal left ventricular function, RV septal pacing appears to be hemodynamically superior to RV apical or RV free wall, and somewhat inferior to left ventricular-only pacing. This relatively subtle difference may partially explain the results of the pacing mode trials (DANISH [31], CTOPP [32], MOST [33], etc.) that required long duration follow-up to show a difference. Note that those trials were all performed in relatively healthy populations. Also, these data may explain why the acute and short-term randomized pacing site trials had equivocal results [57].

In sharp contrast to the above data, the data shown in figure 3 are from another patient in the same study [56]. This patient, with severe left ventricular dysfunction, shows an increased sensitivity to pacing site. Note the distortion in the baseline (AAI) loop compared to the previous figure, indicative of left ventricular dysfunction. Imagine if this patient had received chronic pacing at the RV apex!

The negative inotropic effect [4,40,41,58] secondary to RV apical pacing has been confirmed using magnetic resonance imaging (MRI) tagging techniques to be secondary to abnormal activation and contraction of the heart [59]. In addition, RV pacing has a disadvantageous effect on maximum venous consumption uptake and cardiac efficiency [60]. These data may further clarify the dramatic results of the DAVID trial, because the ICD population studied in that trial had poor left ventricular function [29].

Numerous acute and chronic clinical studies have been conducted to compare the hemodynamic differences between RV-apical-paced and RV outflow tract (RVOT)-paced patients, yet the results vary. However, unlike the pacing mode trials, most of these studies were in small and varying populations with no precise verification of the actual lead placements in the RVOT and, importantly, follow-up in most trials was quite short [61].

What are the alternatives? While from the previous results it appears that RV pacing in general is deleterious, this is
not true. There is data to suggest that pacing at or near the His-Purkinje system can normalize left ventricular electrical and mechanical activation [62]. Dr. Wiggers [2] stated that the shorter the distance for the impulse to travel to reach the Purkinje system, the more effective the contraction. During direct ventricular stimulation, the contralateral ventricle contracts more effectively than the stimulated ventricle. Contraction patterns can be normalized with pacing despite increased dispersion of activation; duration of contraction is not affected with pacing [39]. Once the electrical activation reached the Purkinje system, the remaining fibers are activated quickly. This is different from LBBB, while electromechanical delay was longer but contraction time was shorter with pacing [63].

Recognition of the chronic adverse effects of RV pacing has stimulated interest in strategies to either reduce or attenuate these effects. Of the approaches listed, each one, with the exception of perhaps the managed ventricular pacing (MVP) and AAISafeR modes, has inherent risks and/or programming interlocks associated with programmable parameters associated with it. There are several conventional approaches to minimization of ventricular pacing. These are single chamber AAI(R) pacing, which eliminates the possibility of ventricular pacing with its attendant risks and consequences; VVI(R) pacing which eliminates the possibility of AV synchrony and physiologic chronotropic support; and manipulation of dual chamber mode timing cycles to minimize unnecessary ventricular pacing at the RV apex. Finally, new, unconventional approaches to manage ventricular pacing via smart “modes” such as the MVP and AAISafeR modes which operate as smart mode switch algorithms that continuously monitor loss or restoration of conduction and can dynamically switch between AAI(R) operation and DDD(R) operation.

### Alternate Site Pacing

The ultimate objective of pacing is to achieve chronic restoration of normal cardiac function. Over the decades, several tools have been developed to achieve this goal, including pacing algorithms, devices, and leads. Selective site RV pacing has been suggested as an approach to reduce the incidence of ventricular dysfunction, atrial arrhythmias, and to influence morbidity resulting from asynchronous left ventricular activation emanating from traditional RV apex pacing. Pacing from the RV apex allows a stable ventricular rate and enables reproduction of AV synchrony but does not reproduce physiologic activation of the left ventricle. Studies have also demonstrated that lead placement in non-traditional atrial sites reduces the frequency of symptomatic atrial tachyarrhythmia episodes, especially when combined with preventive algorithms [64]. For wider adoption of selective right atrial and RV site pacing, the pacing community will require reliable benchmark clinical outcomes trials and validation of the ability for safe and efficient implants.

Cardiac pacing was envisioned originally to treat hemodynamic instability thought to result from a lack of cardiac output due to a low ventricular rate. Advances in the field of cardiac physiology have established that cardiac output is not dependent solely on ventricular rate, but the combination of a physiologic heart rate, atrial contribution, and left ventricular activation sequence, all impacting upon the function of the left ventricle. Cardiac pacing utilizing electrical stimulation has evolved in an attempt to reproduce these physiologic parameters and hence to re-establish physiological left ventricular function. Extrinsic electrical stimulation can be defined in four principal targets: re-establishing stable heart rate, restoring AV synchrony, achieving chronotropic competence (rate-response) and normal physiologic activation and timing patterns. All four of these targets are based on the expectation that safe and reliable electrical therapy is available at all times.

**Target 1: Re-establishing the heart rate.** Initially, the goal of pacing was establishment of a stable ventricular rhythm. Early pacing candidate patients had AV block and were treated with single site ventricular pacing. Initially, pacing was limited to a fixed rate due to available technology, but technological advancements evolved to allow demand pacing. Pacing lead technology initially required epicardial placement, but evolved to allow endocardial implants with reliable electrical performance and stability in the RV apex [1,54,65,66].

**Target 2: Restoring AV synchrony.** Developments in amplifier and sensing technology, along with improvements in lead design and materials, created the first opportunities for restoring AV synchrony. This was achieved by either pacing the atrium or sensing and tracking its intrinsic activity. Either of these events triggered a programmable duration of AV delay after which, if intrinsic ventricular activity was not sensed, the lower chamber was paced. These developments resolved most cases of pacemaker syndrome and offered physiologic rate variation for those patients with a stable, trackable atrial rhythm. Unfortunately, these attributes also opened the door to a new problem: pacemaker-mediated tachycardia. Also, although the atrium could be paced, no therapy was available for atrial fibrillation. At the time, the phrase “physiologic pacing” [66] was coined but, in retrospect, use of the term may have been premature, particularly for patients with a high degree of heart block.

**Target 3: Achieving chronotropic competence (rate-response).** Sensors that detected the need to change pacing rates enabled pacemakers to respond to patient metabolic needs and improved patient exercise capacity. The quality of life benefits of these sensor-driven, rate-responsive devices were quickly demonstrated. With the introduction of rate response, the technical issue of delivering an electrical charge that depolarizes the atria and ventricles at the appropriate time has been resolved from a practical standpoint. However, this
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The use of selective pacing sites may achieve this goal and may result in improved left ventricular performance with reduction or avoidance of left ventricular remodeling [69]. Selective site pacing additionally may reduce atrial tachyarrhythmias.

The fourth goal, three of the four stated targets: establishing stable and physiologic activation and timing patterns. Examination of some long-term effects of pacing from traditional sites has begun to reveal non-physiologic aspects of current approaches. Producing normal heart rates and AV delays on the surface ECG is not enough. We must now look closely at the entire depolarization pattern through all four chambers of the heart, as well as the functional effects of stimulating and sensing from different sites within the atria and ventricles. Initiation of electrical activation in the right atrial appendage may result in significant activation delay for the left atrium, with consequent effects on timing between left atrial and left ventricular contraction. Pacing the ventricles at the RV apex compounds this effect. In addition, ventricular contraction patterns associated with pacing at the RV apex can exhibit significant variations in ventricular muscle strain as well as left/right discoordination and longer depolarization times [35].

Recent clinical data have demonstrated that RV apical pacing alone, independent of pacing mode, can lead to left ventricular dysfunction. In the DAVID trial [29] it was noted that in ICD recipients with prior left ventricular dysfunction, low rate (40 bpm) single chamber ventricular pacing (VVI-40) was associated with less deleterious effects than dual chamber pacing at a nominal rate of 70 bpm (DDDR-70). Additionally, the MOST trial [30,49], in which all RV leads were placed at the apex, revealed that single-chamber atrial pacing in patients with sick sinus node was associated with a lower incidence of hospitalization related to symptoms of congestive HF than patients who received dual-chamber pacemakers. Similarly, in a prospective 3-year follow-up study by Nielsen et al [68], it was reported that patients with sick sinus node randomized to DDDR pacing, independent of AV delay, exhibited increased left atrial dilation and a higher incidence of atrial fibrillation, compared with those patients randomized to single-chamber atrial pacing. So, the need for alternate site pacing is obvious. Current technologies in cardiac pacing have successfully met three of the four stated targets: establishing stable and physiologic heart rate, and enabling AV synchrony. The fourth goal, achieving normal physiologic activation and timing patterns has yet to be attained. The use of selective pacing sites may achieve this goal and may result in improved left ventricular performance with reduction or avoidance of left ventricular remodeling [69]. Selective site pacing additionally may reduce atrial tachyarrhythmias.

Pacing Sites: Traditional, Alternate and Selective. Traditionally, the right atrial appendage and RV apical pacing are used as pacing sites because they allow easy endocardial placement of leads while providing stable and reliable chronic pacing parameters. Although these sites maintain heart rates and AV synchrony, RV apical pacing is associated with increased morbidity and mortality relative to native AV conduction [29,30,41,45,49,68]. Right ventricular apical pacing initiates an abnormal asynchronous electrical activation pattern which results in asynchronous left ventricular contraction and relaxation [4,45-47,70]. Consequently, RV apical pacing can lead to inhomogeneous left ventricular wall strain [42], myofibrillar disarray [43,44,71], and pathological perfusion defects [3,4,42,70] with resultant increases in congestive HF and mortality.

The term “alternate site pacing” refers to sites other than the right atrial appendage or RV apex. Implicit with the phrase “alternative site pacing” was the false notion that one was opting to alter from a proven standard care pacing; i.e., RV apex or right atrial appendage. The term “selective site pacing” has been proposed as more accurately reflects the physician’s rationale for where he chooses to implant a pacing lead(s). The physician selects a specific pacing site for a variety of potential benefits. In the atria, the specific site is selected to reduce intra-atrial conduction delays and minimize dispersion of refractoriness which improves clinical syndromes and their associated disease states such as refractory atrial tachycardias and paroxysmal atrial fibrillation, as well as reduction of other adverse effects of traditional pacing [72]. These include improvement of depolarization patterns, hemodynamics, sensing and efficacy of atrial tachyarrhythmia/atrial fibrillation therapy. Site selection also allows minimization of far-field right wall sensing. In the ventricles, expected improvements from a more physiologic depolarization pattern include better hemodynamics [61], less mitral valve regurgitation and less remodeling [73], as well as delaying, reducing, or eliminating long-term negative changes such as perfusion defects and heart failure [55,70].

STANDARDIZATION OF SELECTIVE SITE PACING

Numerous acute and chronic clinical studies have been conducted to compare the hemodynamic differences between RV apical and RVOT paced patients, yet, the results vary. It should be noted that in only one study was it found that RVOT pacing was hemodynamically worse than RV apical pacing [61]. Among 17 studies (acute and chronic) comparing the hemodynamic differences between RV apical and RVOT paced patients, 8 studies favor RVOT pacing; 1 study had negative results for RVOT vs RV apical pacing, while 8 studies found no difference between the two sites. Why do the
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results vary? There are many differences among the studies: varied patient populations, non-physiological pacing (VVI not DDD), arbitrary AV delays in DDD pacing (similar for RV septal and RV apex pacing; normally there is a 30-50 ms delay in conduction between these sites), co-morbidities, varied or unknown EF and QRS duration. But the most important factor seems to be the location of the ventricular paced lead. The term RVOT is used arbitrarily and the location in RV septum and RVOT is unknown, which means a precise, uniform definition is needed.

As researchers have attempted pacing from other areas of the heart, they have been hindered by the lack of uniform definitions of preferred pacing sites and the inadequacy of tools to consistently reach those locations and verify correct placement [69]. In addition, this lack of definition consensus may have contributed to the apparent conflict of data. Without these advances, variations between patients will make proving the advantages of selective site pacing difficult, if not impossible. Therefore, there is need for standardization of terms and identifying measures for selective pacing sites.

Traditionally, when defining new pacing sites in the heart, the literature has defined anatomical positions. These sites are very difficult to visualize and verify using electrophysiology laboratory tools. There is a need to correlate anatomical sites with fluoroscopy and EGG tracings. Thus, using tools available at implant and in the electrophysiology laboratory, the physician is able to accurately reach and verify selective pacing sites. Using selective site pacing, a variety of additional sites in the atrium or ventricle may be used for lead placement to achieve various potential benefits.

Right Atrial High Septum: To address improvement of physiological activation and perhaps prevent atrial fibrillation, leads may be placed at the high right atrial septum, either in the crista terminalis or in Bachmann’s bundle, a group of muscular fibers that originate in the crista terminalis. This atrial muscle tissue has high conduction velocity but lacks distinct electrophysiological properties. EGG criteria for this approach are positive or isoelectric P waves in leads II, III and aVF.

Right Ventricular Outflow Tract (RVOT): The implanting electrophysiologist and cardiologist have rather loosely used the term RVOT to refer to a poorly defined broad area of the RV, which has come to include all areas except for the RV apex.

RVOT Anatomical Definition: We define the lower border of the RVOT as a line drawn parallel to the RV inferior border, extending from the apex of the tricuspid valve (His) to the border of the RV in an antero-posterior (AP) view. The anatomical RVOT upper border is defined as the pulmonary valve. These boundaries form a trapezoid-shaped area, whose remaining borders would be the interventricular septum and RV free wall in the left anterior oblique (LAO) view. Utilizing standard fluoroscopy, one cannot visualize the exact RVOT landmarks provided by the described anatomical model. Therefore, one must use fluoroscopic images and EGG patterns that would correlate with these same areas defined by the anatomical model.

RVOT Fluoroscopic Definition: The RVOT anatomical lower border is demarked on fluoroscopy by extending a pacing catheter parallel to the RV inferior border from the tricuspid valve apex (His) to the RV border in the AP or right anterior oblique (RAO) view. This catheter correlates with the lower border of the anatomical RVOT. The upper border of the anatomical RVOT is determined on a fluoroscopic image by positioning a pacing catheter through the pulmonic valve (noted by loss of R-wave on the intracardiac electrogram). The junction of the RV and pulmonary artery is identified by the appearance of large R-waves as the catheter is withdrawn into the right ventricle. This correlates with the pulmonic valve, which is the upper border of the anatomical RVOT. The above method demonstrates how to correlate the anatomically defined RVOT via a fluoroscopic image. The next goal is to define specific anatomical sites within the RVOT area.

Defining Specific RVOT Sites: For simplicity, the RVOT can be divided into four quadrants. The RVOT is divided horizontally in half by a line halfway between the pulmonic valve and lower border (connected from the RV septum to the RV free wall), forming an upper and lower half. The RVOT is divided vertically in half by a line that connects the pulmonic valve to the RVOT lower border; i.e., dividing the RVOT into a RV septal and RV free wall area. This classification defines high and low RVOT septal positions and high and low RV free wall positions. The LAO 400 fluoroscopic view is utilized to help differentiate the RVOT septum and free wall (Figures 4-6). EGG confirmation of pacing in the RV septum is manifested by a negative QRS morphology in lead I (Figure 5), whereas pacing in the RV free wall manifests as a positive QRS morphology in lead I. Use of the RAO view helps to guide high and low positions. A high position will result in an upright QRS in aVF, and lower positions will have less positive QRS deflections in aVF (Table 1, Figure 5).
FIGURE 4. An LAO 30° view during ICD implantation in one of our own patients. The active fixation right ventricular (RV) pacing/defibrillation lead is located in the low septum of the RV outflow tract (see text for details).

FIGURE 5. An LAO 30° view during biventricular pacemaker implantation and alternate site right ventricular (RV) pacing, in one of our own patients. The active fixation RV lead is located in the low septum of the RV outflow tract (RVOT). This site was selected and confirmed by fluoroscopy and ECG criteria (QRS complex negative in lead I and isoelectric in lead aVF). Note the width of the QRS complex in the 12-lead ECG, it is almost normal (at baseline the patient had a QRS >180 ms). Coronary sinus venography is presented where the target vein (lateral branch) is easily accessed with use of an over-the-wire left ventricular (LV) lead system. The combination of RV alternate site pacing and biventricular pacing has not been examined in the literature, but according to our experience it seems to work better.

**Benefits of Alternate Site Pacing**

**Atrial Tachyarrhythmias**

Significant data have already demonstrated that lead placement in the atrial septal site reduces the frequency of symptomatic atrial tachyarrhythmia episodes, especially when combined with prevention algorithms [64]. It has also been shown that high septal lead placement delays the time to development of chronic atrial fibrillation [72]. Additional research indicates the use of atrial septal lead placement may reduce P-wave duration and decrease the dispersion of refractoriness [74]; may reduce AV conduction time and potentially facilitate more intrinsic conduction [74], and may prevent paroxysmal atrial fibrillation in symptomatic patients who are refractory to antiarrhythmic drugs [75]. Other benefits are also being investigated. It is believed atrial anti-tachyarrhythmia pacing should be more effective from the atrial septal site since it is closer to the left atrium. It is thought that many atrial flutters are atypical and originate from the left atrium. In addition, detection of atrial tachyarrhythmias may be better from the atrial septum, as it may reflect true atrial tachyarrhythmia. Right atrial appendage electrograms tend to be more organized and stable, while right atrial appendage leads are more likely to classify atrial fibrillation as atrial tachycardia for this reason.

Based on current data, it is anticipated that the standard of care will use lead placement in the mid/high region of the atrial septum for a variety of benefits. However, the ability to explore specific atrial pacing sites may result in modified recommendations in the future.

**Ventricular Hemodynamic Performance:** The use of RV selective site pacing could be more beneficial than the RV apical pacing currently used for treating bradycardia. Potential negative effects of RV apical pacing have been discussed as early as 1925 [2,38,76], and a recent trial has indicated that RV apical pacing should be avoided [29]. Abnormal activation patterns that result from RV apical pacing can cause changes in collagen and myocardial fibrous tissue content, resulting in remodeling and cellular damage. Over a period of several years, left ventricular dysfunction and cardiac failure can occur. In contrast, RV selective site pacing in the RVOT/septal region may provide better therapy including more physiologic depolarization and activation patterns in both the atrium and

**Table 1. QRS morphology related to different RVOT sites**

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<tr>
<th>RV Alternate Site Pacing</th>
<th>Lead I</th>
<th>Lead aVF</th>
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<tbody>
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<td>High Septal</td>
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<td>Low Septal</td>
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RV= right ventricle; RVOT= right ventricular outflow tract
IATROGENIC LBBB/ALTERNATE SITE PACING

The introduction of paced rhythms with QRS durations greater than 120 ms has proven the value of tailoring a patient's depolarization pattern for each individual patient. In the area of resynchronization, the opportunity to select pacing sites and optimize therapy for every individual patient in the area of resynchronization has proven the value of tailoring a patient's depolarization pattern for each individual patient. In the area of resynchronization, the opportunity to select pacing sites and optimize therapy for each individual patient. In the area of resynchronization, the introduction of biventricular pacing for heart failure has proven the value of tailoring a patient's depolarization pattern for each individual patient.

FIGURE 6. Here is shown alternate site pacing in the right atrium (interatrial septum) and the right ventricle with direct His bundle pacing, in a patient with sick sinus syndrome and normal left ventricular (LV) function. In both chambers active fixation pacing leads of novel technology (lumenless/steroid-eluting) are used in both chambers. The fluoroscopic view is shown in (c) and (d) in anteroposterior (AP) and left anterior oblique (LAO) 30° views respectively. In (a) and (b) AAI and DDD pacing are shown. Note the narrow QRS complex during DDD pacing with short AV delay. The patient did not have AV conduction disturbances (Kappos KG, Manolis AS, et al: unpublished data).

Some of the variability in the results of these studies can be given conflicting and controversial results. However, attempts to evaluate the clinical impact of alternative pacing sites suffer from a paucity of clinically relevant criteria to quantify this impact. Most studies published so far use relatively “soft” surrogate endpoints (e.g., quality-of-life, 6-minute walking test, NYHA classification, acute hemodynamic impact, QRS width, etc.). These parameters are not considered by many as sufficiently robust for exact quantification of the true clinical benefit, and mortality data are not available on a larger scale. This should not be considered as a weakness of the study but rather as a reflection of lack of parameters allowing for a more subtle evaluation of the severity of the syndrome of heart failure in its course in an individual patient.

Schwaab et al [87] showed in an acute study that QRS narrowing produced by RVOT pacing compared with RV apical pacing was associated with homogenization of left ventricular activation and an increase in left ventricular systolic function. A similar acute hemodynamic improvement produced by RVOT pacing was described by Giudici et al [78]. De Cock et al [88] observed superiority of RVOT pacing in terms of the cardiac index in patients without structural heart disease. However, some patients with a reduced left ventricular EF < 0.50 or advanced coronary artery disease had a decreased cardiac index during RVOT pacing. In contrast, Buckingham et al [89] demonstrated only nonsignificant increase of dP/dt during single site RVOT and simultaneous RV apical and RVOT pacing as compared with single site RV apical pacing.

During mid-term follow-up, Victor et al [82] found neither substantial change in functional class nor hemodynamic benefit during RVOT pacing compared with RV apical pacing. Conversely, Tse et al [70] compared both types of stimulation at 18 months and demonstrated that patients with RV apical pacing presented more often with pacing-induced regional wall-motion abnormalities than those with stimulation of the interventricular septum corresponding with the RVOT. Interestingly, no significant difference in prevalence of regional wall-motion abnormalities was present earlier during follow-up (at 6 months).

There are three possible explanations for these mixed results: (1) a short duration of follow-up could explain the inconclusive results of previous clinical studies; (2) the lead position in the RVOT could have also influenced the results. The exact position was not explicitly specified in some of them. Of note, most of the previously mentioned studies described lead position using x-ray images and only some of them identified the final lead position using pacing-induced QRS width [70, 82, 87, 89]. The pacing lead in these studies was implanted in the region with the narrowest QRS complex during pacing. (3) Finally, pacing-induced acute changes in hemodynamic performance do not necessarily predict hemodynamic improvement during long-term pacing.

Some of the variability in the results of these studies can be

ventricle [3,35,44]. Selective site pacing could be particularly beneficial for young patients, active elderly patients and those patients with left ventricular dysfunction, offering the clinician the opportunity to select pacing sites and optimize therapy for each individual patient. In the area of resynchronization, the introduction of biventricular pacing for heart failure has proven the value of tailoring a patient's depolarization pattern by choosing the appropriate activation site(s). For other pacing patients, it must be determined whether selective site pacing will improve left ventricular performance by maintaining synchrony. A better understanding of left atrial activation is needed in order to predict its improvements in left atrial and left ventricular timing and its contribution to left ventricular filling. The combination of synchrony and a physiologic activation sequence may lead to improved hemodynamics.

REVIEW OF PRIOR STUDIES ON ALTERNATE RIGHT VENTRICULAR PACING SITES

Introduction of newly designed active fixation (screw-in) pacing electrodes has enabled lead implantation into different regions of the right ventricle [69]. In an effort to identify an optimal pacing site that will not worsen cardiac function, alternative sites within the right ventricle have been proposed: (1) RVOT, septal [77] and in the free wall [78, 79], (2) the His-bundle [80, 81], and (3) bifocal RV pacing [61, 82-86]. The results of studies evaluating alternative pacing sites in the RV have
explained by the strong likelihood that different investigators were pacing at different sites in the RVOT. Based on mapping data, it appears that when you pace from the higher RVOT, you are farther away from the His-Purkinje system. The ideal position seems to be pacing from the mid-septum, where the earliest endocardial signal, often with a potential from the right bundle can be observed. This is at the level of the His-Purkinje system or lower (i.e., the beginning of the RVOT). This is reflected by the narrowest QRS complex as compared to the RV apex or high RVOT pacing (Figure 6).

In contrast, pilot studies evaluating combined pacing at more than two sites demonstrated a positive impact of multisite pacing on cardiac output in patients after cardiac surgery [90] or with congestive heart failure [91]. The results of such studies evoked interest in biventricular pacing.

Stambler et al [85] conducted a randomized, crossover multicenter study of RVOT pacing compared to RV apical pacing. This trial included 103 patients with chronic atrial fibrillation and EF <0.40 with 3 months of pacing at each site and quality-of-life endpoint. RVOT pacing shortened the QRS duration in this study, but did not improve quality-of-life or other clinical outcomes. This study had a follow-up period that was shorter than that used in the trials of left ventricular pacing [92-102]. Using a Cochrane search strategy, nine studies of RVOT pacing were identified by de Cock et al [65]. The results of these studies (217 patients) were pooled and showed a significantly better hemodynamic effect (odds ratio 0.34) compared to RV apical pacing. This suggests that this approach may offer a mildly beneficial effect compared to ventricular pacing at the standard location.

**HIS-BUNDLE PACING**

His bundle pacing has been of theoretical interest for many years. The idea of delivering a pacing impulse directly into the cardiac conduction system is attractive because of the possible hemodynamic benefits that could be obtained by a normal activation sequence. However, the small size and anatomic position of the His bundle have made this approach difficult. The first attempts at direct His-bundle pacing were performed in dogs and used transthoracic access [103,104]. Transvenous His-bundle pacing in humans was performed for the first time in 1970 using a multipolar catheter [105]. However, catheter instability during cardiac contraction and para-Hisian pacing presented significant challenges. In 2000 and 2004, Deshmukh et al [62,80] described a significant reduction of left ventricular end-systolic and end-diastolic diameter, improvement of left ventricular EF, and in NYHA class during permanent direct His-bundle pacing in 14 patients with a narrow QRS (<120 ms), chronic atrial fibrillation, and depressed left ventricular EF (<0.40). Hemodynamic improvement could be substantially influenced by rate control and rhythm regularity, more than by pacing site. Another important question is if the patients with chronic HF and intraventricular delay will benefit from His-bundle pacing as much as from biventricular or single site left ventricular pacing. Yamauchi et al [106] showed decreased mitral regurgitation and improved hemodynamics acutely using direct His bundle pacing. In addition, Vazquez et al [107] have published a multipatient study validating the concept and duplicating the findings by Deshmukh et al. In an effort to improve the success rate of direct His bundle pacing, echocardiography has been used to guide the permanent pacemaker lead to the region of the His-bundle. Although this has been successful in animals [108], only temporary pacing has been achieved in humans [109]. Figure 6 shows such a case of direct his bundle pacing from our department. Future studies and wide acceptance of this pacing site would depend on the development of better tools, including delivery systems and specialized leads with possibly a longer helix capable of stimulating not only the His-bundle but the His-Purkinje system on the right and left side of the septum.

**DUAL SITE (BIFOCAL) RIGHT VENTRICULAR PACING**

Besides anecdotal reports, there is only one medium sized study (n=39) in patients with dilated cardiomyopathy and conventional pacemaker indication for chronic AV block which found a significant and remarkable improvement in systolic and diastolic left ventricular function together with a reduction in QRS duration when pacing from the RV apex and the RVOT simultaneously [110]. Other systematic approaches to bifocal RV stimulation in patients with different degrees of left ventricular dysfunction did not show significant improvement over single site pacing either from the apex or the RVOT [85,89,111-113]. This applies to hemodynamic measurements and quality of life scores. The only consistent finding was a shortening of the QRS duration if increasing numbers of RV sites were paced together [111]. Although there was a significant correlation between the changes in paced QRS and cardiac output with dual site stimulation [112] in one report, this did not transfer into a beneficial effect for the whole group. In a recent study [114], a single-center experience was reported with CRT utilizing a protocol that specifically required the implantation of a bifocal RV lead system when pacing could not be adequately achieved from a lateral left cardiac vein. They found that, when biventricular CRT cannot be achieved, a bifocal RV system confers similar benefits at 6 months [114]. CRT increases AV, as well as inter- and intra-ventricular synchrony. In the acute setting, the bifocal RV system can be expected to have similar effects on AV synchrony. This particular study [114] showed an immediate decrease in degree of mitral regurgitation with the bifocal RV system, perhaps from greater interventricular synchrony, in particular at the level of the interventricular septum. The bifocal RV system is not capable of recruiting the delayed lateral wall of the left ventricle. This was evidenced by the less pronounced improvement in wall motion observed with the
bifocal RV system than with the biventricular system, a clear deficiency of this approach. At 6 months, however, overall resynchronization improves with the bifocal RV system, perhaps from ventricular remodeling. The authors concluded that their nonrandomized observational study suggests that clinical improvements conferred by biventricular stimulation can be matched in selected patients by implanting a bifocal RV system. While the bifocal RV system should not be chosen as an initial treatment method, it may be an acceptable alternative in patients who have undergone unsuccessful left ventricular lateral vein implantation attempts (Figure 7) [114].

CONCLUSION AND RECOMMENDATIONS

Selective site pacing [116] may help achieve the long-term goal of normal physiologic activation and timing patterns. In addition, it may address the challenges that can result from traditional pacing. While critical research lies ahead, this technological breakthrough holds significant promise.

Where does this leave us? More chronic studies with more selective patient criteria are needed. Access and placement of leads in the RVOT/septum is feasible. When RVOT was used for pacing because the apex was inadequate (perforation, high threshold, diaphragmatic stimulation, problematic sensing, etc.), there was no lead-related electrical differences from apical pacing. Location of leads in alternate sites needs to be better documented. Antero-posterior and oblique images are needed to compare sites. Role of paced QRS duration in hemodynamic function needs clarification. More data are needed to confirm contribution of AV delay to hemodynamic function with alternate site pacing. Individual optimization may be the best approach. Patients with normal ventricular conduction distal to the AV node may show most benefit.

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