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Alternate Site Pacing in Patients at Risk for Heart Failure

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Cardiac pacing from the right ventricular apex is the most common site of cardiac pacing. During the last decade, several studies demonstrated the harmful effects of the iatrogenic left bundle branch block, which is observed in cardiac pacing from the right ventricular apex. These observations led to an interest in alternative right ventricular pacing sites aiming to achieve a more “physiological” pattern of ventricular activation. Alternate site pacing may involve His bundle, other right ventricular sites (outflow or septal sites), or left ventricular sites in either unifocal or bifocal or biventricular modes. Pacing from the right ventricular outflow tract has been studied extensively. Several studies showed that right ventricular outflow tract pacing has better hemodynamic effects and less harmful influence. Bifocal right ventricular (apical and outflow tract) pacing has been proposed for patients with heart failure where the coronary sinus approach to effect biventricular pacing turns out to be unsuccessful because of various reasons. Some studies examined left ventricular pacing alone as an alternative mode of pacing, and the results were quite encouraging but not conclusive. Finally, in heart failure patients not responding to biventricular pacing, the triple site pacing mode has been recently proposed. In triple site pacing, the leads are inserted in the right ventricular apex and outflow tract in conjunction with lateral left ventricular pacing. Improvement of exercise capacity and increased ejection fraction were observed with this triventricular pacing. Although more data from specifically designed randomized studies are needed, there are many alternative pacing sites, especially for patients at high risk of heart failure, which seems to be less harmful and better tolerated by the patients.

Keywords: right ventricular outflow tract pacing; left ventricular pacing; triventricular pacing; iatrogenic left bundle branch block

From the early 1960s, the right ventricular (RV) apex has been the traditional site for positioning of transvenous endocardial pacing leads. The apex allows easy accessibility, short fluoroscopy times, stable lead function, and a low incidence of complications. Cardiac pacing from the RV apex produces a characteristic wave of depolarization, which results in abnormal ventricular activation from the apex to the base and from the right to the left ventricle, resulting in an increased total ventricular activation time with pronounced late activation of the lateral left ventricular (LV) wall. This type of depolarization is similar to that observed in left bundle branch block (LBBB). During the last decade, several studies demonstrated the harmful effects of this pacemaker-induced LBBB, which is observed in cardiac pacing from the RV apex. These harmful effects include LV dysfunction,1 heart failure,2 atrial fibrillation (AF),3 and higher mortality rates.4

The exact pathophysiologic mechanisms underlying the detrimental effects of RV apical pacing are not fully understood and seem to be multifactorial. The hemodynamic effects of pacing-induced LV electromechanical dyssynchrony were implicated to explain the above-mentioned clinical observations.5 Furthermore, the activation of the sympathetic nervous system, the functional mitral regurgitation, and the abnormalities in myocardial histopathology are also possible incriminatory factors.6 All these observations led to an interest in alternative RV pacing.
sites in order to achieve a more “physiological” pattern of ventricular activation.

Alternate Sites of Ventricular Pacing

It remains controversial whether there is an optimal site for RV pacing. Alternate site pacing may involve His bundle, other RV sites (outflow or septal sites), or LV sites in either unifocal or bifocal or biventricular (BiV) modes.

His Bundle Pacing

Theoretically, His bundle pacing mimics the physiological way of RV depolarization. Pacing the proximal His-Purkinje system may restore ventricular chronotropic competence and preserve a normal pattern of ventricular activation in the absence of intraventricular conduction disturbances. Although demonstrated in animal studies since 1967, its use has been limited because of difficulties regarding consistent and reliable capture. There are only small clinical studies that examined the efficacy of His bundle pacing. Deshmukh et al8 reported a significant improvement in LV function in 12 patients with heart failure and chronic AF with permanent, direct His bundle pacing. The same investigators applied direct His bundle in 39 heart failure patients with persistent AF and after a follow-up period of 42 months, the majority of the patients (29 of 39) presented improved LV performance.9 In another study of 16 patients with chronic AF, undergoing atrioventricular nodal ablation, an active fixation lead was inserted in the para-Hisian position, along with a lead at the RV apex.10 Patients were randomized into two 6-month crossover periods: standard RV apex pacing or para-Hisian pacing. There was a non-significant trend toward a reduction in LV end-diastolic volume with para-Hisian pacing compared with RV apical pacing, and a similar trend for an increase in LV ejection fraction (LVEF) (53.4% ± 7.9% compared with 50.0% ± 7.9%). Moreover, there was an increase in 6-minute walk distance with para-Hisian pacing (431 ± 73 vs 360 ± 71 meters (m), P < .05).

Right Ventricular Outflow Tract (RVOT)

The area of the RVOT seems to be the most interesting because it is easily accessible during implantation, and the use of an active fixation electrode provides stable localization and reduces the risk of dislocation. For these reasons, RVOT has been more extensively studied. Giudici and Karpawich11 defined 4 sites in the RVOT: (a) RV infundibular septal pacing: above, on, or beneath the annulus of the septal/anterior tricuspid valve leaflets; (b) RV inlet septal pacing: pacing proximal to the pulmonic valve distal to or near the crista supraventricularis; (c) RV outflow septal pacing: pacing near the septal/moderator band insertion on the RV septum; (d) RV apical septal pacing: pacing proximal to the septal moderator band continuity. A pooled analysis of 9 prospective studies evaluating the hemodynamic effects of RVOT pacing in 217 patients indicated a modest but significant hemodynamic benefit compared with RV apical pacing (odds ratio: 0.34).12 From this pooled analysis those who did not have apical pacing for comparison, those using epicardial rather than endocardial leads, and studies performed in heart failure patients were excluded. Among these studies, the majority reported acute hemodynamic effects, while only 2 studies reported long-term hemodynamic effects. One of these studies showed no difference between the 2 sites after 3 months of follow-up in patients with chronic atrial tachyarrhythmias and complete atrioventricular (AV) block,13 and the other reported a significant increase in LV fractional shortening (31% vs 26%, P < .01) following 2 months of RVOT pacing.14 The largest study included in this analysis compared the acute hemodynamic effects of RV apical and outflow tract pacing in 89 patients.15 Cardiac output was improved by 19% at the time of implant in 85 patients by pacing the outflow tract (from 6.6 ± 2.4 at the apex to 7.8 ± 2.9 L/min at the outflow tract; P < .001), while cardiac index improved by 21% (P < .0001).

More importance must be given to studies comparing chronic pacing at the RVOT compared with the apex, as the problems associated with RV pacing appear to be a time-dependent phenomenon. Except the 2 studies mentioned above, there are an additional 4 studies that prospectively examined the medium to longer-term effects of pacing at these sites on LV ejection fraction (LVEF) as one of their outcome variables. Two of these studies compared the 2 sites in the same patients using a crossover design with the patients acting as their own controls,18,19 and the other 2 studies randomized patients to RVOT or RV apical pacing at time of implant.16,17 Two of these studies17,19 support the hemodynamic advantage of RVOT pacing. In the first one, 24 patients with a standard pacing indication to AV sequential pacing underwent implantation of a ventricular lead in either
the apex or septum of the RV.\textsuperscript{17} It is the only published study that has examined the effect of ventricular pacing site in the presence of AV synchrony. In addition there was a relatively long follow-up period of 18 months. This extended follow-up period may explain why this study came up with positive results while others did not provide the same results, despite similarities in the design and methodology, as there were no significant differences at 6 months. Outcome measures were EF and perfusion defects on radionuclide ventriculography. The second study\textsuperscript{19} included 28 patients after ablation of the atrioventricular junction for permanent AF, followed by implantation of a DDDR pacemaker connected to 2 ventricular leads. The lead that was placed at the septum was connected to the atrial port, and the lead that was placed at the apex was connected to the ventricular port. Septum or apex was paced by programming AAIR or VVIR modes, respectively. Patients were randomly assigned 4 months later to pacing at one site for 3 months, then crossed over to the other for 3 months. Septal pacing was associated with shorter QRS (145 ± 4 vs 170 ± 4 milliseconds; \( P < .01 \)). At 3 months, among patients with baseline LVEF ≤ 45%, LVEF was 42% ± 5% after septal pacing versus 37% ± 4% after apical pacing (\( P < .001 \)). On the other hand, in another study\textsuperscript{16} enrolling 20 patients, there were no significant differences in systolic function between pacing sites. The ROVA (Right Ventricular Outflow Versus Apical Pacing) study,\textsuperscript{18} the only randomized study comparing RVOT with apical pacing, examined 103 patients with heart failure and chronic AF. Although outflow tract pacing shortened the QRS duration, it did not consistently improve quality of life compared with RV apical pacing at the short-term follow-up of 3 months.

In a single-center registry published in 2006,\textsuperscript{20} data from 460 consecutive patients who had a ventricular lead implanted at RVOT were reported. The overall success rate in the RVOT was 84% over the total 9-year period, with a 92% success rate in the last 4.5 years. At 20 months, in a subgroup comparison of RVOT and right ventricular apical (RVA) implants (73 patients), there was no significant difference in pacing threshold, R-wave sensing, or pacing lead impedance. In symphony to these results, we also reported studying 30 patients in whom alternate site pacing was evaluated, in whom the success rate of implantation was 93% with excellent measurements obtained acutely and during 1- and 3-month of follow-ups.\textsuperscript{21}

**Bifocal Right Ventricular Pacing**

Bifocal RV (apical and outflow tract) pacing has been proposed for patients with heart failure where the coronary sinus approach to effect BiV pacing turns out to be unsuccessful due to various reasons, such as failure to cannulate the os or to advance the lead, absence of a suitable venous tributary to place the lead, phrenic nerve stimulation, or failure to pace or sense due to scarred tissue. The long-term (for a 22-month period) clinical response of 22 patients undergoing this approach has been favorable with ensuing clinical improvement.\textsuperscript{22} Similar results were reported for 39 patients with New York Heart Association (NYHA) class III symptoms of heart failure requiring permanent cardiac pacing for AV block.\textsuperscript{23} In the ROVA study,\textsuperscript{18} in a subset of 50 patients with NYHA class II-III after 3 months of dual-site RV pacing, physical functioning was worse (\( P = .04 \)) than during RVA pacing, mental health was worse (\( P = .02 \)) than during RVOT pacing, and NYHA functional class was slightly better (\( P = .03 \)) than during RVOT pacing. In another small study, the clinical improvement conferred by ventricular pacing (44 patients) was similar with the improvement seen in 6 patients after bifocal RV pacing.\textsuperscript{24} In the Bifocal Right ventricular stimulation (BRIGHT) study\textsuperscript{25} 42 patients with EF < 35%, QRS width ≥ 120 milliseconds, an LBBB and NYHA class III and IV, were studied. Compared with baseline, bifocal pacing improved EF from 26% ± 12% to 36% ± 11% (\( P = .0008 \)), NYHA classification decreased from 2.8 ± 0.4 to 2.3 ± 0.7 (\( P = .007 \)), the 6-minute walk test improved from 372 ± 129 m to 453 ± 122 m (\( P = .05 \)), and the Minnesota Living with Heart Failure scores decreased from 33 ± 20 to 24 ± 21 (\( P = .006 \)). Eight patients did not tolerate reprogramming from bifocal to control pacing (programmed to an inactive mode), with symptoms disappearing in all patients after reprogramming to bifocal pacing.

**Biventricular or Left Ventricular Pacing**

A few studies have compared RV apical pacing with LV or BiV pacing, which has now become the standard method to apply cardiac resynchronization therapy in patients with refractory heart failure.\textsuperscript{26-30} The Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (PAVE) trial was a randomized trial of 190 patients, in which the benefits of BiV pacing over RV apical pacing were evaluated.\textsuperscript{31} In this study from baseline to 3 months,
both groups showed an improvement in hall walk exercise capacity, but after 3 months, only patients in the BiV group maintained their functional capacity. The latter group also experienced significant improvement in peak VO₂ and exercise duration. Left ventricular EF remained stable in patients with BiV pacing, while it declined significantly in the RV pacing group during 6 months (from 45% to 41%).

**Exclusive Left Ventricular Pacing**

As alluded to earlier, RV apical pacing may not be necessary even for patients receiving BiV pacing. There are few studies that examined the acute hemodynamic effects of LV pacing alone in comparison with RV and BiV pacing. In 27 patients with heart failure, having an epicardial LV lead indicated that LV pacing alone was superior to RV pacing, but also to BiV pacing as well.³² In another acute hemodynamic study in 18 heart failure patients, LV pacing yielded the best hemodynamic response compared to both RV pacing and BiV pacing.³³ The clinical efficacy of single-site LV pacing was assessed in 86 patients with heart failure. Left ventricular pacing significantly improved exercise tolerance (VO₂ peak increased 2.46 mL/min/kg [P < .001], the anaerobic threshold increased 1.55 mL/min/kg [P < .001]), the distance walked in 6 minutes increased by 47 meters (P = .024), and the quality-of-life score improved 8.1 points (P = .004) in the patients with QRS >150 milliseconds.³⁴ In the Bi vs Left Ventricular Pacing: an International Pilot Evaluation on Heart Failure Patients with Ventricular Arrhythmias (BELIEVE) study,³⁵ 74 patients with heart failure were studied and were randomized to either LV or BiV pacing. After the 12-month follow-up period, the percentage of responders was comparable for both groups (LV = 75%, BiV = 70%; P = .788). Moreover, LV pacing induced significant LVEF increase (5.2%; P = .002), and there were no differences in the numbers of ventricular arrhythmias, hospitalizations, and death events between the 2 pacing modes. In the Optimal Pacing Site (OPSITE) study,³⁶ 56 patients participated and primary endpoints were quality of life and exercise capacity, which were modestly improved mainly by BiV, rather than LV, pacing.

**Triventricular Pacing**

In heart failure patients not responding to BiV pacing, it has been proposed that triple site (TRIV) pacing may be beneficial. A common way to achieve TRIV pacing is to implant the pacing leads at the RV apex, the RVOT, and the LV through the coronary sinus. In a recent study,³⁷ this technique was performed in 26 patients, and after 3 months, a significant reduction (P < .05) of NYHA class, improvement of exercise capacity, and increased EF were observed. In a preliminary study recently published,³⁸ 54 heart failure patients were enrolled and randomly assigned to either BiV or TRIV mode of pacing. After 3 months, TRIV was associated with a more significant (P < .05) NYHA class reduction, increase in VO₂ max (2.9 vs 1.1 mL/kg/min) and 6-minute walking distance (98.7 vs 51.6 m) than conventional biventricular pacing. The response rate in the TRIV group was 96.3% vs 62.9% in the conventional group (P = .002), and the authors suggest that upgrade to triple-site pacing may be considered in nonresponders to standard resynchronization therapy. Finally, in a crossover study,³⁹ 26 candidates for cardiac resynchronization therapy were randomly paced with TRIV or dual-site BiV stimulation. After 3 months, no significant difference in quality of life or in 6-minute hall walk was observed between the 2 groups. However, a significantly higher LVEF (27 ± 11% vs 35 ± 11%; P = .001) and smaller LV end-systolic volume (157 ± 69 vs 134 ± 75 cm³; P = .02) was observed with triple-site pacing.

In conclusion, RV apical pacing is the most common site of lead positioning in the majority of patients receiving pacemakers. Right ventricular apical pacing is, however, a nonphysiologic substitute for intrinsic ventricular activation over the His-Purkinje system. Several studies suggest that this form of cardiac stimulation may even be harmful, particularly in patients who do not require ventricular pacing and suffer from dysfunction of the left ventricle. All these data have pushed the investigators to determine new approaches to cardiac pacing beyond the conventional methods and techniques.

**References**


