Interventricular septal or standard apical pacing in pacing dependent patients: still a dilemma?

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BACKGROUND

Permanent ventricular pacing for symptomatic bradycardia is one of those treatments proved to change the lives of numerous patients faced with a disease with high morbidity and mortality. Because of the important benefits of cardiac pacing in these patients, possible disadvantageous effects on cardiac function have only recently been recognized. Among possible ventricular pacing sites, right ventricular apex (RVA) has been selected as the conventional site. RVA site is easy accessible, allow safe and stable long-term pacing (1). More than 80 years ago, in 1925, Wiggers showed that RV pacing was associated with a reduction in left ventricular (LV) function (2,3,4).

Despite of important advantages, RVA pacing generates LV dyssynchrony, hemodynamic impairment, diastolic and systolic dysfunction with or without heart failure, especially for pacing dependent patients (5). This pacing site determines an abnormal contraction pattern bypassing normal conduction tissue (6). LV dyssynchrony has important hemodynamic impact on LV function, with increased morbidity, mortality, risk of heart failure, and atrial fibrillation (7). This high risk of heart failure was observed even in patients with normal cardiac function before pacing (8).

The most important goal in cardiac pacing is to achieve a less eccentric, more physiological activation and timing patterns. In order to keep a normal cardiac function in patients with permanent ventricular pacing, an alternative pacing site might be superior to RVA (9). Septal RV pacing (IVS) might be an alternative site, because it is associated with shorter QRS duration than anywhere else in the RV (10) (Figure 1).

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ANATOMIC CHANGES IN RVA PACING

Right ventricular (RVA) pacing bypasses the His-Purkinje system resulting in a LBBB-like pattern on the surface ECG. In LBBB the activation of the RV precedes the LV, but on the normal way (11). During ventricular pacing, the impulse conduction occurs predominantly through the working myocardium. RV is first activated antero-apical, followed by trans-septal activation of the LV. The remaining part of the LV is activated slowly (12,13). The resulting electrical asynchrony generates a prolonged QRS duration due to slow myocardial conduction, greater then in the LBBB. The LV contraction is altered, and a significant inter- and intraventricular dyssynchrony may occur (14). The impact of pacing on ventricular activation pattern depends also on intrinsic conduction disturbance (15,16).

Ventricular dyssynchrony due to RVA pacing results in abnormal late activation of lateral wall, LV remodeling, asymmetric hypertrophy and redistribution of cardiac mass (17,18), delayed papillary muscle activation with valvular insufficiency (19-21), increased left atrial diameter (22), and reduced myocardial perfusion and EF (23,24).

There are important redistribution of strain and coronary blood flow with RVA pacing. Early activated regions have ≈ 60% blood flow of late activated regions. The regions activated via the Purkinje system have greater fiber strain and blood flow (25,26). All these myocardial changes were observed to be present after more than 3 years (27). All important changes generated from RV pacing and the relationships between them are summarized in Table 1 and Figure 2.

DEFINITION OF THE SEPTAL SITE

The RV septum is a relatively large area. Thus, the IVS pacing consists of a heterogeneous group of different pacing sites.

Giudici and Karpawich (28) defined the location of ventricular lead and the ECG generated patterns:

- **RV Inlet Septum**: “Above, on, or beneath the annulus of the septal/anterior tricuspid valve leaflets. Relatively normal QRS morphology and axis.”
- **RV Infundibular Septum**: “Proximal to the pulmonic valve distal to, or near, the crista supraventricularis. Left bundle branch, vertical axis.”

By using the 2D echocardiography as the “gold standard” to visualize the exact pacing lead, Ng et al. defined different locations for IVS pacing sites.

The insertion sites for the RV pacing were visualized in the parasternal short-axis views, and were confirmed in the subcostal and apical views.

Septal anterior pacing was considered achieved if the tip of the pacing wire was seen inserting at the septoparietal trabeculations in the high ventricular or midventricular anterior segments.

RV septal pacing sites other than the anterior septoparietal trabeculations (i.e., midseptal, posteroseptal, RV free wall, or true RV outflow tract) were defined as septal nonanterior pacing.

RV apical pacing was considered if the pacing wire was seen inserting into the RV apex, as visualized in the short-axis view at the LV apical level.
SITE SELECTION – AN IMPORTANT DILEMMA

Clinical impact

There are limited data on the long term clinical outcome after RV pacing in patients with acquired AV block. In UKPACE (29) the annual incidence of HF was low, with 3.2% in the single-chamber pacing group, and 3.3% in the dual chamber pacing group, after a mean of 3 years of follow-up. The optimal RV pacing lead location for patients with standard indication for ventricular pacing is still controversial.

In a study of all factors that predict high mortality in permanent pacing patients, effect of chronic RVA pacing on left ventricular function was found to be the strongest predictor of LVEF decrease (5).
To prevent the detrimental hemodynamic effects of long-term RV pacing, alternative pacing sites have been studied. There is often a debate whether LV dysfunction after long term ventricular pacing is real or is dependent on pre-existing disease. A wide QRS complex before implantation may carry a higher risk of developing HF with right ventricular pacing (30).

The adverse effects on ventricular structure explain the association of RVA pacing, with increased risks of AF, heart failure (4, 9), and death in randomized clinical trials (22-32).

Recent studies have shown that up to 31–53% of pacemaker patients had LV dysfunction, and RVA pacing can lead to adverse outcome (5,32). The DAVID trial provided additional evidence that right ventricular pacing was associated with an increased risk of death and heart failure hospitalization in patients with an impaired LV function selected for ICD therapy (4). New or worsened heart failure or death during 3 years of follow-up was seen in 50% of patients with RVA pacing with >50% ventricular pacing (3).

Freudenberger et al. analyzed 11,246 patients with apical pacing. After a long follow up, a significantly higher hospital admission rates and cardiac death were observed compared to a control group.

Pacing from the IVS has been studied extensively, considered to have better hemodynamic effects and less harmful influence. This site of pacing generates an activation pattern very different, not as good as intrinsic conduction, who seems to improve outcomes, both acutely (39,40) and medium term (41,42).

A retrospective analysis of 150 consecutive patients, who underwent pacemaker for symptomatic bradycardia, showed that IVS pacing improve medium- and long-term survival. Vlay found, in a 9 year experience of 460 consecutive implants, an overall success rate of 84% in the IVS group, with excellent lead performance.

However, long-term clinical data are limited to nonrandomized studies or investigations including relatively few patients, heterogeneous groups, and different methods of evaluation (1,37). Furthermore, most studies that compared RV septal with apical pacing used echocardiographic or radionuclide determination of LVEF or acute invasive hemodynamic parameters. Follow up periods in these studies ranged from acute effects to up to 18 months.

**HISTOLOGICAL AND ECHOCARDIOGRAPHIC CHANGES**

In a quantitative review of 9 studies, on alternative RV pacing sites, a modest but significant hemodynamic benefit was observed for IVS pacing as compared with conventional pacing (Table 2) (1).

Speckle-tracking analysis revealed that permanent RV pacing induced heterogeneity in time-to-peak radial strain, resulting in LV dyssynchrony in 57% of patients. A short time-to-peak radial strain of the anteroseptal segments and a long time-to-peak radial strain of the posterolateral segments were found. These findings were associated with deterioration of LV systolic function, and NYHA functional class (32).

After a mean of 3.8 years of follow up, in patients with normal LV function and no evidence of intraventricular or interventricular dyssynchrony at baseline, Tops et. al (34) found that 50% of these patients have developed new-onset echocardiographic evidences of dyssynchronism. Similar to these findings, other long-term studies (35, 36) concluded that RVA pacing induced ≈ 5-10% absolute reduction in LVEF, in patients with baseline preserved LV function.

RVA pacing impairs cardiac output, stoke work, EF, LV relaxation in patients with or without LV dysfunction (36). The decrease in LV systolic function and NYHA functional class is directly related to the presence of LV dyssynchrony (32). The effects of RVA pacing were found to be greater in patients with impaired LV function (33).

There are some studies that suggested the benefic role of the alternative ventricular pacing site. Karpawich et al. in a histological study compared RV apical with mid-septal site. He shown prevention of remodeling with IVS pacing after 4 months follow-up. No calcification, degenerative changes, or altered mitochondrial morphology were observed in the septal paced group (Figure 3).

Tse et al. (35) revealed that the mean QRS duration was significantly longer during RVA than IVS pacing. At 6 and 18 months after pacing, the incidence of myocardial perfusion defects and regional abnormalities were higher, and LVEF was lower (47±3 vs. 56±1%) during RVA than IVS pacing. He concluded that preserved synchronous ventricular activation during
INTERVENTRICULAR SEPTAL OR STANDARD APICAL PACING IN PACING DEPENDENT PATIENTS: STILL A DILEMMA?

IVS pacing prevented the long-term deleterious effects of RVA pacing on myocardial perfusion and function in patients with permanent pacemakers.

The exactly time course of development of LV dyssynchrony, LV dysfunction, and heart failure is still unclear. The dysfunction of right ventricle is the first abnormality that occurs in RVA paced patients, which manifests by 1 week. This is followed by LV dysfunction which starts by 1 month. The diastolic dysfunction precedes the systolic dysfunction in both ventricles (43).

Despite the theoretical advantage of the IVS pacing, numerous reports did not show convincing data of the superiority of IVS over RVA pacing.

Kypta et al. (37) analyzed 98 pacing dependent patients regarding LVEF, BNP levels, and exercise capacity at 3 days, 3 months, and 18 months after the implantation. All changes from baseline to 18 months were statistically not different between septal and apical stimulation.

Riedlbauchova et al. (44) found a significant beneficial effect in positioning the RV lead in the mid ventricular septum, especially in the patients with non-ischemic cardiomyopathy.

**TABLE 2.** Haemodynamic variable from different studies, identified by comprehensive search; De Cock, CC et al. Europace 2003; 5:275-278

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication/year</th>
<th>No. of patients</th>
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CO, cardiac output; T, thermodilution; E, Echo-Doppler study; N, nuclear study; FAC, fractional area change; PACE, Pacing Clin Electrophysiol; JACC, Journal of the American College of Cardiology. For details of publications see reference list. Results: +, positive effect; −, negative effect; ±, no effect of right ventricular outflow-tract pacing as compared with apex pacing.

**FIGURE 3.** Histological differences after 4 months, between apical and septal site. No morphological changes were observed in the septal group (adapted from Karpawich PP et al. Am Heart J 1991; 121:827-833)
These results were not confirmed by other investigators who did not observe similar results in comparable study cohorts (45).

Cate et al. (46), in an acute study of patients with normal EF and without other cardiac abnormalities, concluded that both RVA and IVS pacing increase in the same way electromechanical delay compared to no pacing. Both can negatively affect regional longitudinal LV strain and timings without differences. Ng et al. (47), in a long-term study demonstrated more impaired circumferential strain and worse LV dysynchrony in septal than in apical pacing and control. Liu et al. (48) revealed an acute increase of the LV systolic dysynchrony index assessed with real-time 3D echocardiography during RVA pacing in a group of patients with sinus sick syndrome.

Occhetta et al. used a stimulation site which we consider the most proximal to the HIS bundle of all cited studies. He reported excellent results showing a similar QRS complex during intrinsic ventricular activation (52).

An important point is the specific position in the IVS pacing. Lieberman et al. (36), pointed out that the different positions of the septal lead could explain the different results reported in the literature. Ng et al. confirmed that RV septal pacing consists of a heterogeneous group of different pacing sites.

Another interesting point is that, there is no evidence to suggest that LV function will be reduced by non-RVA pacing. The non-inferiority of septal pacing could become an argument for the use of this pacing site. 

CONCLUSION

The optimal RV pacing in patients with a standard indication for ventricular pacing is still controversial. Different positions in the septum, and different evaluated parameters might explain the conflicting data about hemodynamic impact of this site when comparing to apical pacing. The effects of RV pacing could be attenuated by considering the importance of underlying cardiac disease. It is conceivable that patients with a significant LV activation delay may be at risk of developing LV dysfunction.

Echocardiography offers a remarkable variety of techniques and measurements with no clear gold standard for the characterization of LV dysynchrony or for prediction of clinical response.

We think that larger studies and longer follow up, including selected patients, and comparing only specific septal sites to conventional pacing, might reveal more clear differences between these pacing sites, with clinical implications. We also suggest that a “gold standard” method for the evaluation of these patients is also important.

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