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Permanent Cardiac Pacing in Adults with High Grade Atriovetricular Block and Preserved Left Ventricular Function: Optimal Mode and Site of Pacing

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1. Introduction

Cardiac pacing is the only effective treatment for patients with sick sinus syndrome and atrioventricular conduction disorders. In permanently paced patients, cardiac performance and exercise capacity depend on 3 main parameters: the quality of chronotropic function, atrioventricular synchrony, and the ventricular activation sequence.

Dual chamber pacing is believed to have an advantage over single chamber ventricular pacing in that it resembles cardiac physiology more closely by maintaining atrioventricular (AV) synchrony and dominance of the sinus node, which in turn may reduce cardiovascular morbidity and mortality thus contributing to patient survival and quality of life.

However, the prospective studies designed with the objective of analyzing the impact of maintaining AV synchrony on mortality were disappointing. The PASE (Lamas et al, 1998), CTOPP (Connolly et al, 2000), MOST (Lamas et al, 2002) and UKPACE (Toff et al, 2005) studies demonstrated only secondary benefits, such as the decrease in the incidence of atrial fibrillation and improved quality of life, but without any effect on mortality. It has been proposed that the probable deleterious effects of right ventricular stimulation leading to dyssynchrony can annul the benefits obtained with the atrioventricular synchronism. At the same time, there is increasing evidence that conventional pacing from the right ventricular apex was associated with dyssynchronous activation of the left ventricle, resulting in impaired haemodynamic function (Leclercq et al,1995;Wilkoff et al,2002; Schmidt et al, 2007; Tops et al, 2006; Tops et al, 2007).

The detrimental effects of ventricular apical pacing on left ventricular (LV) haemodynamics were demonstrated as early as 1925 by Wiggers (Wiggers, 1925). However, it was not until recently that it became abundantly clear that the time has come to seek alternative ways to minimize or avert the adverse clinical outcomes resulting from the asynchronous contraction pattern that RVA stimulation induces (Wilkoff et al, 2002; Tops et al, 2007, Sweeney et al,2003).

In this Chapter, we attempt to discuss in patients with high grade atrioventricular block and preserved LV function, 1) the optimal mode of pacing (VVI(R)= single chamber, ventricular pacing in the inhibited mode vs DDD=dual chamber pacing and sensing, both triggered and inhibited mode) particularly in elderly patients, 2) the effectiveness and safety of alternative

RV pacing, 3) to compare the effects of alternative RV pacing to RVA pacing on electric and mechanic LV synchrony, systolic and diastolic LV function and outcomes.

2. Pacing mode selection

The pacemaker prescription has the greatest impact on procedural time and complexity, follow-up, patient outcome, and cost: the choice among single-chamber ventricular pacing, and dual-chamber pacing. In 2008, revision of the "ACC/AHA/NASPE Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices" have updated the previous versions published in 1984, 1991, 1998, and 2002 (Epstein et al ,2008). These guidelines have included sections on selection of pacemakers in patients with atrioventricular block (Figure 1).

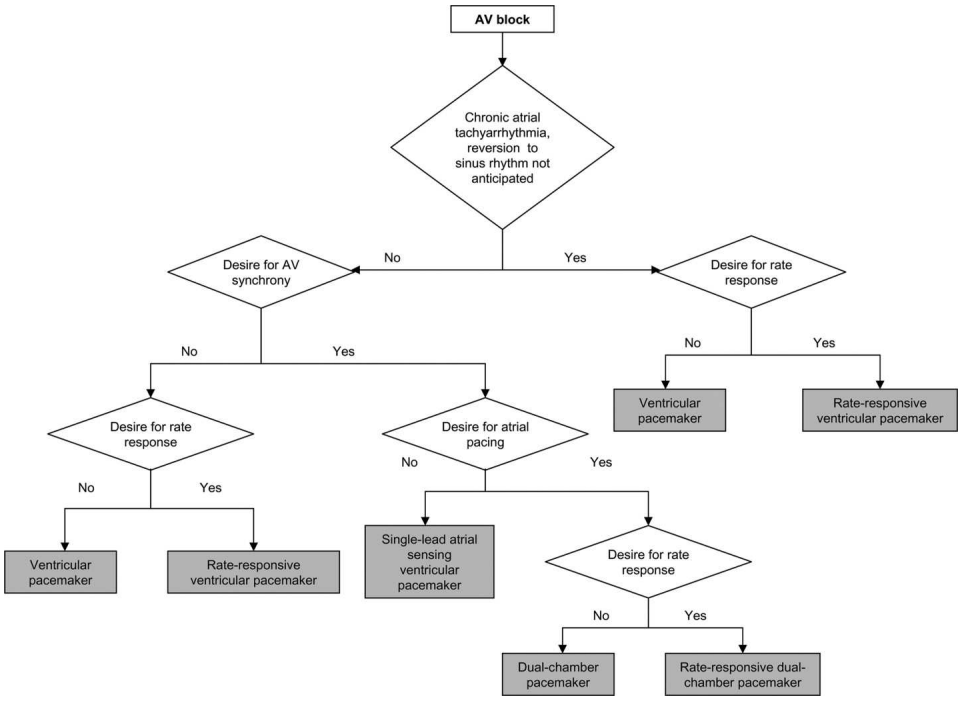

Fig. 1. Selection of Pacemaker Systems for Patients With Atrioventricular Block. Decisions are illustrated by diamonds. Shaded boxes indicate type of pacemaker. AV indicates atrioventricular. (Epstein et al,2008).

As with all clinical practice guidelines, the 2008 recommendations have focused on treatment of an average patient with a specific disorder and may be modified by patient comorbidities, limitation of life expectancy because of coexisting diseases, and other situations that only the primary treating physician may evaluate appropriately.
Augmented life expectancy and increasing health care expenditures have led to questions concerning the routine use of electrotherapy in elderly patients. More than 80% of pacemaker recipients are aged > 65 years. So the selection of the pacing system has

important clinical and economic implication. Despite the results of randomized trial (Lamas,1998; Connolly, 2000; Toff, 2005), the use of dual chamber systems, continues to provoke debate particularly in elderly. The several randomized clinical trials such as PASE (Lamas et al,1998), CTOPP (Connolly et al, 2000), MOST (Lamas et al, 2002), and UKPACE (Toff et al, 2005) demonstrated that DDD pacing (dual chamber pacing and sensing, both triggered and inhibited mode), is not superior to VVI (R) pacing (single chamber, ventricular pacing in the inhibited mode with or without rate responsive) in the prevention of death and stroke in patients with conduction disease.

UKPACE (Toff et al, 2005) is a prospective multicenter,randomized, parallel-group trial comparing the clinical benefits of ventricular pacing and dual-chamber pacing in elderly patients with AV block. In this population, the pacing mode does not influence the rate of death from all causes during the first 5 years or the incidence of cardiovascular events during the first 3 years after implantation of a PM. These findings have questioned the justification for implantation of DDD (R) pacing mainly in elderly patients. Unfortunately, a subgroup analysis (Jahangir, 2003) based on pacemaker dependency has not been presented for either the MOST or UKPACE.

Several previous studies have compared dual chamber pacemaker (DDD) and rate-responsive ventricular pacemaker VVIR pacing in elderly patients, and they showed an improvement in symptom scores and objective exercise performances (Jordaens et al,1988; Hargreaves et al,1995; Channon et al,1994). Most studies have demonstrated that the haemodynamic benefits of DDD pacing during maximal exercise result largely from the increase in heart rate rather than from atrioventricular synchrony (Kritensson et al, 1985; Faerestrand & Ohm,1985; Buckingham et al, 1992; Fananapazir,1985). Rate responsive ventricular demand (VVIR) pacing may therefore represent an alternative to DDD pacing in the elderly.

In a recent study published by our institution, we (Ouali et al, 2010) have demonstrated in elderly population (over 70 years) with dual chamber pacemakers inserted for complete AV block, significant benefit from DDD pacing compared with VVIR pacing. There were improvements in HR-QOL questionnaire (SF36), NYHA functional class and echocardiographic parameters. On the contrary, the 6 min walking distance was similar in the two groups.

In this study, 36,6 % of patients deteriorated in NYHA functional class during VVI R pacing (from NYHA class 2,1 ± 0,6 to NYHA class 2,5±0,5), a rate which is consistent with previously published results from studies of a similar design (Naegeli et al, 2007; Rediker et al, 1988; Heldman et al, 1990). Hargreaves et al (Hargreaves et al, 1995) demonstrated that in their elderly population (over 75 years), both total and pacemaker syndrome symptom scores were significantly lower during DDD mode compared with VVI and VVIR modes. However, both exercise performance and the perceived level of exercise (Borg scores) during DDD and VVIR modes were similar. In the opposite, Oldroyed et al (Oldroyed et al,1991) have not identified significant differences between pacing mode (VVIR, and DDD) in patients with complete AV block, in symptoms scores for dyspnea, fatigue, exercise time and maximal oxygen consumption. However, resting plasma concentrations of atrial natriuretic peptide were raised in complete heart block and were restored to normal by DDD pacing but not by VVIR pacing ((Oldroyed et al,1991).

Frielingsdorf et al (Frielingsdorf et al, 1995) have showed that in patients with normal left ventricular function, may profit most from preserved AV synchrony (VDD = ventricular pacing with atrial tracking vs VVIR) as shown by the higher maximum uptake on exercise

and conclude that rate responsive single chamber pacemakers largely enable the same work capacity as dual chamber pacemakers in patients with high degree AV block.

Elderly patients are assumed to have a more sedentary lifestyle, and consequently to have less need for physiological pacing. On the other hand, haemodynamic studies have shown that the atrial contribution to ventricular systolic function becomes more important with advancing age (Kuo et al, 1987; Miller et al, 1986). Hoïijer et al (Hoïijer et al, 2002) showed improved cardiac function and quality of life following upgrade to dual chamber pacing after long-term ventricular stimulation in 19 patients (age: 75,5 ± 7,3 years) with AV block or sinus node disease. Left ventricular systolic function was significantly superior in the DDDR mode (mean aortic velocity time integral; P<0,001) and left atrial diameter was significantly smaller in the DDDR mode than in VVIR mode (P=0,01). The plasma level of brain natriuretic peptide was significantly lower in DDDR pacing (p=0,002)

Considering ventricular systolic function, Ouali et al (Ouali et al, 2010) have demonstrated decreased LV-EF and myocardial systolic velocities assessed by Tissue Doppler Imaging following VVI pacing, results which are in agreement with those of previous studies in which non physiologic pacing was found to affect the LV contractile efficiency negatively (Naegeli et al,2007; Höijer et al, 2002).

Naegeli et al (Naegeli et al,2007) showed that patients experience a highly significant, two to three fold increase of BNP and NT-proBNP levels during VVI(R) pacing compared with synchronized atrioventricular pacing which was reversible after restoring AV synchrony. So the authors (Naegeli et al,2007) suggested that the loss of atrioventricular synchrony, while on VVI(R) pacing is directly responsible for increased levels of natriuretic peptides, most likely as a result of increased atrial and ventricular stretch and pressure (Levin et al, 1998). These subtle improvement in haemodynamic performance detected by natriuretic peptides in AV pacing was associated with a mild but significant increase in left ventricular ejection (p=0,036). These mild changes in left ventricular function may not be clinically relevant, but need to be interpreted with regard to the short periods in these different studies.

The subjective response to VVI(R) pacing is highly dependent on whether there had been previous exposure to dual chamber pacing. Since having a pacemaker implanted, whether it be VVI(R) or DDD(R), results in a great improvement in quality of life compared to having an untreated AV block or sinus node disease. All paced patients are likely to feel considerably better, making it difficult to ascertain which group improved the most.

DDD pacing preserves AV synchrony, but disturbs inter and intra-ventricular synchrony resulting from RV pacing like VVI. Echocardiographic data have demonstrated inter and intra-ventricular dyssynchrony as assessed by interventricular delay and the aortic pre ejection period (152,6±23,1ms vs 151,4 ± 25,3 ms) in the two pacing modes (ouali et al, 2010). The hemodynamic deleterious effect via RV apical pacing could be exaggerated in elderly patients, in whom reduced ventricular compliance is frequently present (Connolly et al, 2000).

Even elderly, patients with complete heart block and sinus rhythm, DDD pacing is associated with improved quality of life and systolic ventricular function compared with VVI pacing. In active elderly patients with complete heart block, efforts should be made to maintain AV synchrony and VVI (R) pacing should not be used instead of DDD pacing.

3. Pacing site selection

Modern pacemakers currently provide pacing modes and algorithms minimizing unnecessary ventricular pacing, but in patients with atrioventricular conduction system

disease in whom a high percentage of ventricular stimulation is mandatory, there is no way to exclude it. Especially for these patients, the need for identification of more 'physiological' pacing sites has become more and more compelling. Right Ventricular Apical permanent pacing could have negative hemodynamic effects. Initially, attention was directed to RV outflow tract/septum pacing and His/para-Hisian pacing in patients with LV dysfunction (Mera et al, 1999; Schwaab et al, 1999; Buckingham et al, 1997; Buckingham et al, 1998; de Cock et al, 1998) and latter in preserved LV function patients (Giudici et al, 1997; Karpawich & Mital, 1997; Kolettis et al, 2000; Bourke et al, 2002; Tse et al, 2002; Occhetta et al, 2006; Victor et al, 2006; Yu et al, 2007; Kypta et al, 2008; Flevari et al, 2009; Ng et al, 2009; Dabrowska-Kugacka et al, 2009; Takemoto et al, 2009; Tse et al, 2009; Gong et al, 2009; Rosso et al, 2010; Verma et al , 2010;106:806-9; Leong et al, 2010; Cano et al,. 2010; Yoshikawa et al, 2010) while subsequently biventricular stimulation began to emerge as an appealing alternative proposal (Yu et al, 2009; Simantirakis et al, 2009; Doshi et al, 2005). Despite attempts to corroborate the theoretical superiority of alternative RV pacing sites, such as septal and His/para-Hisian pacing, the reported outcomes remain conflicting and their efficacy equivocal.

3.1 His/ ParaHissian pacing

Direct His Bundle Pacing (DHBP) was documented as reliable and effective for preventing the desynchronization and negative effects of right ventricular apical pacing. It is, however, a complex method that requires longer average implant times, cannot be carried out on all patients and presents high pacing thresholds (Deshmukh et al, 2000; Deshmukh et al, 2004, Zanon et al, 2006). On the contrary, the parahisian pacing, with simpler feasibility and reliability criteria, seems to guarantee an early invasion of the His-Purkinje conduction system, with a physiological ventricular activation, very similar to the one that can be obtained with direct His bundle pacing (Occhetta et al, 2006).

The parameters that allow for the direct pacing of the His bundle were defined(Deshmukh et al, 2004):

1. the morphology and the duration of the native QRS and the paced QRS must be identical on the 12 standard ECG derivations
2. the HV interval on the original rhythm and the spike-QRS distance in the paced signal must be equal (with a tolerance margin of 10 ms)
3. the pacing threshold must be high (> 2V), since it must capture a specific non-muscular conduction tissue;
4. the pacing lead should be positioned with the distal pole (screw in) at the same level as one of the two electrodes of a mapping catheter on the His bundle (x-ray in both right and left anterior oblique projections)

The criteria for the realization of parahisian pacing are (Deshmukh et al, 2004):

the distal pole of the catheter (screw-in) must be positioned as much as possible next to the mapping dipole of the electrophysiological catheter of reference (within 1 cm in the right and left oblique projections)

1. the duration of the paced QRS can be larger than the spontaneous QRS, but the duration must be at least 50 ms shorter than the QRS obtained with the RVA pacing and, in any case, not more than 120-130 ms.
2. the electrical axis of the paced QRS must be concordant with the electrical axis of the spontaneous QRS;

3. the interval between the spike and start of paced QRS is less than the HV time of the original rhythm;
4. the pacing threshold must be less than 1 V, since the muscular portion of the interventricular septum is paced.

Indication of His or para-His bundle pacing is limited to patients without significant distal conduction abnormalities particularly after ablation of the AV node for chronic atrial fibrillation (Deshmukh et al, 2004, Occhetta et al, 2006).
In these selected patients, His or para-His bundle pacing might be optimal (Zanon et al, 2008; Occhetta et al, 2006) but its feasibility is limited by the technical difficulties (Occhetta et al, 2006; Deshmuck et al, 2000; Deshmuck et al, 2004). His bundle pacing in patients has been shown to result in better hemodynamic performance (Deshmukh et al, 2004) and more uniform distribution of perfusion when compared with RV pacing (Deshmuck et al, 2000). Inversely, Padeletti et al (Padeletti et al; 2007) have demonstrated that acute His bundle pacing did not improve LV function compared with alternate site RV pacing (RVA, RVS and free wall portions of the RVOT) and may be inferior to LV pacing.

3.2 RV septal pacing

3.2.1 Technical aspect of lead implantation for alternative RV pacing site

To attain the septal position, the pacing site was usually determined on a topological rather than functional basis (Giudici & Karpawich, 1999). Different parameters were used variably. In old literature, all authors have used fluoroscopic images, defined as a leftward orientation of the lead confirmed by LAO projection, and considered as the standard approach in the daily practice for a septal site access. Many papers do not define the LAO angle, whereas the Mond papers use 40° (Medi & Mond, 2009). Indeed from experience, it is very hard to manipulate leads with fluoroscopy at 40° either from the left or right sided approach. However, electrocardiographic criteria such as negative deflection of lead I and positive initial R-waves of the paced ventricular complex in leads II and III (Schwaab et al, 2001; McGavigan et al,2006; Lieberman et al, 2004; Balt et al, 2010) or the narrowest paced QRS complex available during the mapping of the interventricular septum (Tse et al, 2002; Tse et al, 2009a; Tse et al, 2009b; Schwaab et al, 2001), were not used uniformly.
Tse et al (Tse et al; 2002) and Mera et al (Mera et al, 1999) have postulated that the paced QRS duration is a practical indicator for determining the optimal RV pacing site. However, Schwab et al (Schwaab et al, 2001) have found the detailed mapping of the RV with precise measurements of QRS duration has been found to be impractical.
This lack of uniform definitions of where the alternate RV sites actually lie and the inadequacy of tools to consistently reach these locations and verify correct placement may account for the variability in lead positioning within the RVS and may have contributed to the mixed results regarding the long-term hemodynamic benefits of RVS pacing (Lieberman et al, 2004; Balt et al, 2010; Iaizzo et al, 2004).
In a recent study, Balt et al (Balt et al, 2010) have concluded that in 143 patients in whom lead implantation in the RVOT was performed, a septal position was achieved in only one-third of patients. The paced QRS complexes resulting from different stimulation sites within the RVOT (anterior, septal, and free wall) were found to differ significantly, but a considerable overlap of QRS patterns was demonstrated, and the authors, could not define clear cut-off point or devise flow-charts to match ECG and pacing site. Differences in ventricular conduction and electrical activation were proposed to explain this overlap (Balt et al, 2010).

Using anatomical reconstruction of the RV in 31 patients to validate pacing sites, Burri et al (Burri et al, 2011) have analyzed and compared 12-lead ECGs wile pacing from a para-Hissian position, from the mid-septum, and from the anterior free wall. The authors (Burri et al, 2011) have concluded that a negative QRS complex in lead I is an inaccurate criterion for validating septal pacing. A negative QRS or the presence of q-wave in lead I tended to be more frequent with anterior than with mid-septal pacing (9/31 vs 3/31, P=0.2 and 8/31 vs 1/31, P= 1, respectively).

In the daily practice, the standard approach of septal site is based generally on only fluoroscopic images during the implantation procedure.

Several studies have demonstrated the feasibility, and the safety of alternative pacing sites (Rosso et al, 2010; Vlay et al, 2006; Medi & Mond, 2009, Schwaab et al, 2001). With active fixation technology, lead placement and stability in the RVS are no longer a problem. Moreover, recently commercially approved stylets (Models 4140, 4150; St. Jude Medical, Sylmar,CA, USA) are available for septal positioning of ventricular leads, which resembles the manually shaped stylet described by the senior author in previous publications (Kypta et al, 2008; Rosso et al, 2010; McGavigan et al, 2006).

In a large study, including 460 patients, Vlay et al. (Vlay et al, 2006) reported on a 9 year experience of right ventricular outflow tract pacing, an excellent success rate and stable lead measurements over time, without an increased risk for acute or chronic complications compared with RVA pacing. There was a reported overall implantation success rate of 84%, with improving success as experience was obtained. Rosso et al (Rosso et al, 2010) have also confirmed that conventional active-fixation pacing leads can be successfully and safely deployed onto the RV septum either in the RVOT or mid RV locations using a purposely-shaped stylet guided only by fluoroscopic views. In this study, it has been quicker to deploy the RVOT lead than the mid-RV lead. Acute electrical parameters for the RV leads at implant were satisfactory, regardless of their positioning at the RVOT or mid-RV septum. The primary success rates of ventricular pacing lead positioning in mid RV septal and RVOT locations were respectively 88.2% and 100% of patients undergoing PM implantation.

In a recent manuscript, Mond (Mond, 2010) have described the implant tools and techniques required for consistent and successful placement of pacing leads onto the RV septum. The PA or approximately 10° RAO projection is recommended. Rather than using the commercial product, the stylet for septal lead placement can be hand prepared at the time of implant. The 40° LAO projection should be performed to confirm septal positioning after the screw deployment. There is at least a 90% success in septal positioning using these techniques with a 97% success rate for the RVOT (Medi & Mond, 2009) with an excellent long-term (1 year) electrical stability in 92 patients undergoing pacemaker implantation for bradycardia indication.

3.2 Electric and mechanic LV synchrony

Since 1925, Wiggers (Wiggers, 1925) have postulated that the longer the distance from the artificial stimulation site to the entry of the His-Purkinje system the weaker the beats that occur. This was supported by the electrophysiological maps obtained in dogs by Lister et al (Lister et al, 1964).

In experimental studies, RVS pacing using a screw-in electrode was shown to produce a synchronous LV electrical activation via stimulation of the genuine intraventricular conduction system deep in the septum, and to prevent the development of adverse cellular changes (Laske et al, 2006; Karpawich & Mital, 1991).

Inversely, in other animal studies (Mills et al, 2009; Peschar et al, 2003), it was demonstrated in canine hearts with normal ventricular conduction that LV function is maintained at SR level when pacing the LV apex or the LV endocardial surface of the interventricular septum (Mills et al, 2009; Peschar et al, 2003) and that electric desynchronization pacing was significantly greater in RV apical and RV septal than LV apical and LV septal pacing (Mills et al, 2009; Wyman et al, 2002). It was also demonstrated by using tagged magnetic resonance imaging that RV apex and RV septal pacing increased significantly mechanical dyssynchrony, discoordination (MRI tagging) and blood flow redistribution (microspheres) and reduced LV contractility, relaxation, and myocardial efficiency (stroke work/myocardial oxygen consumption). In contrast, LV apical and LV septal pacing did not significantly alter these parameters as compared with the values during intrinsic conduction. At 16 weeks, acute intrasubject comparison showed that single-site LV apical and LV septal pacing generally resulted in similar or better contractility, relaxation, and efficiency as compared with acute biventricular pacing (Mills et al, 2009).

In the animal study described by Mills et al (Mills et al, 2009), the lead was implanted in the RV midseptum, based solely on position and not optimizing the QRS complex. Surprisingly, none of the parameters investigated in this study (electric mapping, hemodynamic, regional strains, efficiency) showed a significant difference between RV apical and RV septal pacing. Similarly, no apparent benefit of RV septal pacing over RV apical pacing was observed in a human clinical study of LV pressure-volume loops that also used purely anatomic lead positioning (Lieberman et al, 2006). In the same way, a recent comparison of chronic RV apex and RV septal pacing, based entirely on lead position, showed that RV septal pacing was associated with more impaired circumferential strain and worse LV dyssynchrony than apical pacing (Ng et al, 2009).

In contrast, it has been shown that the RV pacing site, which leads to the best LV function, is not predicted by anatomical position or by QRS duration (Peschar et al, 2003). The hemodynamic superiority of LV apex and LV septum pacing may be explained by a relatively physiological sequence of electrical activation when pacing from these sites (Mills et al, 2009; Peschar et al, 2003).

Some investigators have proposed the idea of a hemodynamic "sweet spot," where each patient has a particular optimal pacing site (Karpawich & Mital, 1997; Tse et al, 2002; Tse et al, 2009 b). The ideal ventricular pacing site should resemble the normal activation and synchronicity of ventricular activation observed with an undamaged conduction system. A pacing site that is in closer proximity with the proximal portion of His bundle at the RV septum should lead to a narrower QRS which in turn might reflect a lesser degree of activation delay compared with RVA pacing (Mera et al, 199; Schwaab et al, 1999; Tse et al, 2002) and less dyssynchrony, as demonstrated by multiple echocardiographic techniques (Tse et, 2002; Flevari et al, 2009; Takemoto et al, 2009; Gong et al, 2009; Leong et al, 2010; Cano et al, 2010).

Pacing on the right ventricular (RV) septum, at high (septal RVOT pacing) (Giudici et al, 1997; Kolettis et al, 2000; Bourke et al, 2002; Tse et al, 2002; Dabrowska-Kugacka et al, 2009; Gong et al, 2009; Leong et al, 2010; Yoshikawa et al, 2010), mid (Yu et al, 2007; Cano et al, 2010; Muto et al, 2007) or lower (Flevari et al, 2009) septal pacing position has been introduced as a potentially favorable alternative to RVA pacing to preserve a more physiologic ventricular activation.

Previous investigations of alternative pacing sites have yielded inconsistent results (Mera et al, 1999; Giudici et al, 1997; Bourke et al, 2002; Victor et al, 2006; Kypta et al, 2008;

Dabrowska-Kugacka et al, 2009; Tse et al Europace 2009; Victor et al, 1999) which may be attributable, in part, to the fact that the pacing site was determined on a topological rather than functional basis (Giudici & Karpawich, 1999).

Many previous studies (Schwaab et al, 1999; Victor et al, 2006; Yu et al, 2007; Ng et al, 2009; Takemoto et al, 2009; Tse et al, Europace 2009, Gong et al, 2009; Leong et al, 2010; Schwaab et al, 2001), have showed that septal pacing induced shorter paced QRS duration than RVA pacing did. These results indicated that RVS pacing resulted in better electric synchrony compared with RVA pacing. However, the duration of the QRS complex was not found to be significantly shorter when pacing from the mid-septum compared with the anterior free wall (Lister et al, 1964).

In 120 consecutive patients with standard pacing indications, Schwab et al (Schwab et al, 2001) have tested the feasibility of RV septal lead implantation technique guided by surface ECG and the degree to which this technique reduces paced QRS duration compared to RV apical stimulation when passive-fixation leads are used. Pace-mapping of the septum was performed until QRS was minimal. QRS could be reduced by 5-55 ms in 83 (69%) of 120 patients. In 22 (18%) patients, QRS was identical with apical and septal pacing, and in 15 (13%) patients, QRS was 5-20 ms (delta QRS) longer despite septal stimulation. Average QRS was significantly shorter during septal pacing compared with apical pacing (151 ± 20 vs 162 ± 23 ms, $P < 0.001$). There was a tendency towards greatest QRS reduction when the high septum was stimulated (22±11 ms reduction) as compared with mid- (18±11 ms) or apical parts of the RV septum (16 ± 10 ms). QRS reduction was most likely if apical QRS width was > 170 ms ($P = 0.0002$), and there was an inverse correlation between apical QRS and delta QRS ($r = 0.53, P < 10^{-7}$).

In the Rosso study (Rosso et al, 2010), two pacing leads were simultaneously and temporarily positioned at the RVOT septum and mid-RV septum in order to determine which pacing site was associated with a narrower QRS. The mean QRS duration in the RVOT septum was similar to the mid- RV septum. The QRS was narrower when pacing from the mid-septal RV in nine patients, whereas it was shorter while pacing the RVOT in three patients . In the remaining patients, there was no difference in QRS duration.

Many recent studies have compared the mechanic synchrony between septal pacing and RVA pacing (Schwaab et al, 1999; Yu et al, 2007; Flevari et al, 2009; Ng et al, 2009; Takemoto et al, 2009; Leong et al, 2010; Cano et al, 2010; Yoshikawa et al, 2010) and have showed a more inter and intraventricular synchrony with septal pacing than apical pacing immediately after implantation and at midterm (after 6 to 12 months of follow-up), excepted for the study of Ng et al (Ng et al, 2009).

Moreover, patients in the RVAP group had significantly more inter and intraventricular dyssynchrony than did the controls, and patients in the RVSP group had comparable values to those obtained from the control group (Flevari et al, 2009; Verma et al, 2010; Cano et al, 2010).

In contrast; Takemoto et al (Takemoto et al, 2009) have revealed that, RVS pacing caused a significant increase in the interventricular mechanical delay (IVMD) compared with AAI pacing, which indicates that the onset of the LV activation is delayed even during RVS pacing. These authors explained that, such an increase in interventricular dyssynchrony may be a result of the initial impulse propagation through a slow muscular conduction region. The increase in the time to peak systolic velocity dispersion among the 12 LV segments (Tsys) during RVS pacing compared with AAI pacing, may also be attributable to the initial delay of the impulse propagation.

Authors measured dyssynchrony by different indices (Flevari et al, 2009; Takemoto et al, 2009; Gong et al, 2009; Leong et al, 2010; Yoshikawa et al, 2010) and available parameters quantifying intraventricular dyssynchrony could not contain all information of dyssynchrony. A positive and statistically significant correlation was found between the paced QRS duration and global dyssynchrony (Victor et al, 2006; Flevari et al 2009; Takemoto et al, 2009; Muto et al, 2007).
However, it has been shown in experimental studies that RV pacing sites maintaining an optimal LV function, are not correlated with the narrowest paced QRS complexes (Peschar et al, 2003). In addition, the correlation between QRS duration and the degree of electromechanical LV dyssynchrony has been disputed (Ng et al, 2009; Bordachar et al, 2003; Tournoux et al, 2007; Bleeker et al, 2004). Using tissue Doppler-derived basal septal-to-lateral wall delay, Bleeker et al (Bleeker et al, 2004) demonstrated a lack of relation between QRS duration and mechanical LV dyssynchrony. In the same way Ng et al (Ng et al, 2009), have concluded that correlations between QRS duration and tissue Doppler-derived systolic dyssynchrony and 2-dimensional speckle tracking-derived circumferential strain dyssynchrony indexes were weak, and there was no correlation with radial strain dyssynchrony (Ng et al, 2009).

3.3 Outcome

Results from acute and chronic studies are summarized in table 1 and show mixed results with a tendency toward better hemodynamic outcome when pacing at these alternative sites (Giudici et al, 1997; Kolettis et al, 2000; Tse et al, 2002; Yu et al, 2007; Flevari et al, 2009; Takemoto et al, 2009; Tse et al, 2009 a; Yoshikawa et al, 2010; Yu et al, 2009; de Cock et al, 2003).

Authors/ year of publication	Study design	N°	Pacing modes	Pacing sites	Septal approach	Conduction disturbances	Paced QRS with alternative RV pacing	Follow-up duration	less VA with RVS than RVAP	Results with alternative RV pacing
Giudici et al, 1997	Not randomized crossover	89	VVI	RVOT vs RVA	NA	14 SSS; 19 intrinsic AVB; 56 AVNA	NA	Acute results	NA	RVOT improves cardiac output
Karpawich & Mital, 1997	Not randomized Crossover	22	VVI/AAI	AAI vs RVA vs RVS	NA	Normal AV conduction	NA	Acute results	NA	RVS pacing, maintained comparable indices with intrinsic and atrial paced rhythms (LV dP/dt, Vmax, and Vpm, and LV end-diastolic pressure)
Kolettis et al, 2000	Randomized crossover	20	DDD	RVA vs RVOT vs AAI	Fluoroscop, ECG, narrowest QRS	Normal AV conduction	Shorter	Acute results	NA	PSP decreased from either site compared with AAI; RVOT is associated with more favorable diastolic function compared with RVA
Bourke et al, 2002	Not-randomized parallel	20	VVIR	10 RVOT vs 10 RVA	fluoroscopy	AVNA AF Narrow QRS	same	23 weeks	±	No major differences were identified in acute or chronic radionuclide parameters of ejection fraction
Tse et al, 2002	Randomized parallel	24	DDD	12 RVA vs 12 RVOT	fluoroscopy and ECG narrowest QRS	Complete AVB Sinus rhythm 75% Wide QRS	Shorter	18 months	+	Best myocardial perfusion and function
Occhetta et al, 2006	Randomized crossover	16[o]	VVIR	Parahissian / hissian vs RVA	ECG Pacing threshold	AVNA; chronic AF; narrow QRS	Shorter	6 months	+	The LVEF did not show any significant differences
Victor et al, 2007	Randomized crossover	28[§]	VVIR	RVA vs RVS	fluoroscopy narrowest QRS	AV node ablation chronic AF	shorter	3 months	NA	chronic RV septal pacing preserved LVEF in patients with baseline LVEF ≤ 45%. No effect in patients with preserved LVEF

Authors/ year of publication	Study design	N°	Pacing modes	Pacing sites	Septal approach	Conduction disturbances	Paced QRS with alternative RV pacing	Follow-up duration	less VA with RVS than RVAP	Results with alternative RV pacing
Yua et al, 2007	Randomized parallel	42	DDD	18 RVA vs 14 RV mid-septal vs 10 AAI	fluoroscopy narrowest QRS	Symptomatic bradycardia	shorter	72 h Acute results	+	better mechanical performance and preserved chronotropic response on myocardial contractility in comparison with apical pacing
Kypta et al , 2008	Randomized Parallel	98¥	DDD	53 RVS (RVOT or midseptal) vs 45 RVA	fluoroscopy and ECG	AV block 55% wide QRS	Shorter	18 months	NA	Changes of BNP levels, LVEF, and exercise capacity s were statistically not different
Flevari et al, 2009	Randomized Parallel	31	DDD	15 Apical vs 16 lower RVS	fluoroscopy ECG	First, 2nd and 3rd AVB 22,5% wide QRS	Shorter	12 months	+	increase in LVEF compared to RVAP
Ng et al , 2009	Not randomized parallel	34	DDD	17 RVS vs 17 RVA vs 22 controls	fluoroscopy	Complete or second AV B QRS duration : NA	Shorter	Median: 692 days	-	RV septal pacing group was associated with poorer long-term LV function
Dabrowska-Kugacka et al, 2009	Randomized parallel	122	DDD, VDD, VVIR	56 Septal RVOT vs 66 RVA	Fluoroscopy	AVB, SSS, AF QRS duration : NA	same	10 years	NA	The RVOT provides no additional benefit in terms of long-term survival over RVA pacing
Takemoto et al, 2009	Not randomized Parallel	55	DDD	40 RVS vs 15 RVA	Fluoroscopy narrowest QRS	AVB/SSS with narrow QRS	Shorter	4 years	+	RVS preserves long-term LV function.
Tse et al , 2009	Randomized Parallel	24	VVIR	12 RVS vs 12 RVA	fluoroscopy and ECG narrowest QRS	Permanent AF bradycardia Narrow QRS	Shorter	24 months	NA	the use of a VRR algorithm with RVS pacing, but not RVA pacing, improved exercise capacity and preserved LVEF
Gong et al, 2009	Randomized Parallel	96	DDD	48 RVOT vs 48 RVA	fluoroscopy and ECG narrowest QRS	AVB Mean QRS duration 97±9 ms	Shorter	12 months	+	no benefit over RVA pacing in aspect of preventing cardiac remodeling and preserving LV systolic function
Rosso et al, 2010	Not randomized crossover	15	VVI	RVOT septum vs mid RVS	fluoroscopy	5 AVB and 12 SSS Mean QRS duration: 0,97±0,23ms	same	Acute results	NA	no preferences in regard to acute lead performance or paced QRS duration with either position.
Verma et al, 2010	Randomized crossover	19*	AAI/ VVI	HRA vs RVS vs RVOT vs RVA vs sinus rhythm	Fluoroscopy and ECG	sinus rhythm Narrow QRS Normal AV conduction	NA	Acute results	+ (RVS vs RVA), ± (RVOT vs RVA)	the RV apex, demonstrated, with the RV outflow tract location, the least mechanically synchronous contraction during
Leong et al , 2010	Randomized parallel	58	DDD	32 RVOT vs 26 RVA	Fluoroscopy and ECG	32 AVB and 26 SSS QRS duration: NA	Shorter	29 ± 10 months	+	superior indices of LV structure and function compared with RVA-pacing, and less adverse LA remodeling.
Cano et al, 2010	Randomized Parallel	81	VVI DDD	28 RVA vs 32 mid RVS vs 21 control	Fluoroscopy ECG	59 AVB and 22 SSS QRS duration : NA	Shorter	12 months	+	No significant differences in terms of clinical outcomes or EF were found
Yoshikawa et al, 2010	Not randomized parallel	60	DDD	36 High RVS vs 24 RVA	Fluoroscopy	40 AVB and 20 SSS QRS duration : NA	shorter	Acute results	+	Left ventricular dyssynchrony was smaller in patients with high septal than apical pacing

AF: atrial fibrillation; AV : atrioventricular; AVNA: AV node ablation; AVB: atrioventricular block; DDD: dual chamber pacing; HRA: high right atrium ; NA: not available; PSP: Peak systolic pressure; RVS: right ventricle septum; RVOT: right ventricle outflow tract; RVA: right ventricle apex; SSS: sick sinus syndrome; VA: ventricular asynchrony; VRR : ventricular rate regularization; VVI: single chamber ventricular pacing; * the study population included only children; § LVEF ≤45% in 12 patients; ¥ LVEF <40% in 14% of patients; ▫ LVEF<40% in 1 patient.

Table 1. Results from studies comparing the alternative right ventricular pacing to RVA pacing in patients with preserved LVEF.

Data from the literature on the RVS vs RVA debate are still conflicting, which might be attributed to the inhomogeneity of the studies performed in different patient populations, differences in trial design (randomized vs not randomized, parallel vs cross-over), the small cohorts studied, the differing protocols used and the lack of accepted definitions of RV lead position, and verifying actual anatomic lead position.

The study patient populations previously published were heterogeneous and consisted of patients with an indication for permanent cardiac pacing because of atrioventricular block with normal or wide QRS duration, sick sinus syndrome or after AV node ablation for permanent atrial fibrillation. These conduction disturbances were not associated with a significant distal conduction abnormalities.

Of the 12 chronic studies (≥ 6 months), 6 demonstrated a significant benefit of RV septal over RV apical pacing (table 1). In 3 of these studies, RV septal pacing produced a shorter QRS duration (Tse et al, 2002; Takemoto et al, 2009; Tse et al, 2009a), whereas in the other positive studies, the septal access was based only on fluoroscopic images and ECG pattern.

Takemoto et al (Takemoto et al, 2009) have concluded that in patients undergoing dual-chamber pacemaker implantation with normal QRS duration (AVB and SND) and preserved LV function at baseline, RVS pacing guided by the paced QRS morphology preserves long-term LV function via minimizing LV dyssynchrony. After a long (~4 years) follow-up period, the LVEF decreased significantly in patients with RVA pacing but not in those with RVS pacing. In this study, paced QRS duration was significantly shorter during RVS than RVA pacing. Tsys dispersion among the 12 LV segments was significantly smaller during RVS than RVA pacing. There was a positive correlation between the paced QRS duration and Tsys dispersion ($R=0.65$, $P<0.0001$). The pacing-induced decrease in LVEF was positively correlated with the degree of Tsys dispersion ($R=0.42$, $P=0.008$).

More recently and in the same way, Leong et al (Leong et al, 2010) have showed in a similar population (AVB and SND and preserved LV function), a significant difference in LV ejection fraction, LV end-systolic volume , and LA volume favoring the RVOT-paced group over the RVA-paced patients after a mean follow up of 29 ± 10 months. RVA-pacing was associated with greater interventricular mechanical dyssynchrony and intra-LV dyssynchrony than RVOT-pacing.

In different studies, Tse et al (Tse et al, 2002; Tse et al, 2009 a; Tse et al, 2009 b) have demonstrated that RV septal pacing improves LV systolic and diastolic function and functional capacity in patients with preserved LV function in different conditions as high grade atrioventricular block (Tse et al, 2002), after AV ablation for atrial fibrillation (Tse et al, 2009 a) or after upgrading in case of previously permanent RV apical pacing (Tse et al, 2009 b). In one particular study (Tse et al, 2002), Tse et al have showed that after 18 months of follow-up in 24 patients with AV block, the group paced from the RVOT presented with fewer myocardial perfusion defects, fewer regional wall motion abnormalities, and an improved LV ejection fraction compared with the RVA-paced group. This finding was attributed to the fact that the detrimental effects of RVA pacing become evident after several months, especially in patients with preserved LV systolic function.

The RV septal pacing also resulted in shorter isovolumic relaxation than RV apical pacing (Yu et al, 2007), implicating better diastolic function that has been invasively demonstrated by Kolettis et al. (Kolettis et al, 2000) at the cardiac catheterization laboratory.

In fact despite the beneficial features of reducing electrical and mechanical dyssynchrony , different studies failed to demonstrate a positive effect on indices of LV structure and

function and did not confirm the above mentioned clinical outcomes, at least during the 3-18 months after implantation (Bourke et al, 2002; Victor et al, 2006; Kypta et al, 2008; Dabrowska-Kugacka et al, 2009; Gong et al, 2009; Cano et al, 2010)

Kypta et al (Kypta et al, 2008) randomized 98 patients with atrioventricular block (AV-block) undergoing pacemaker implantation to positioning the ventricular lead in the high or mid septum (n =53) or in the apex (n = 45) of the right ventricle. The Changes of N-terminal pro-brain natriuetic peptide (BNP) levels, LVEF, and exercise capacity from baseline to 18 months were statistically not different between septal and apical stimulation. The clinical occurrence or deterioration of overt heart failure was similar in both treatment arms. Kypta et al (Kypta et al, 2008) concluded that septal stimulation site is not superior to conventional apical pacing in unselected patients undergoing pacemaker implantation for AVB.

Gong et al (Gong et al, 2009) demonstrated that RVOT pacing did not benefit over RVA pacing in the aspect of preventing cardiac remodeling and protecting LV systolic function after 12 months of pacing in patients with normal cardiac function although it caused more synchronous LV contraction compared with RVA pacing. Inversely Ng et al (Ng et al, 2009) have demonstrated that standard fluoroscopic and electrocardiographic implantation techniques for RVS pacing resulted in a heterogenous group of different pacing sites. They conducted a cross-sectional study in which they compared echocardiographic dyssynchrony and the LV function parameters between RVS (n = 17) or RVA (n = 17) pacing in complete or second AVB patients and a control group of non-paced patients (n = 22). They found that the RVS pacing patients had a lower LVEF, lower circumferential strain, and greater circumferential dyssynchrony despite achieving a narrower QRS complex. They concluded that these detrimental effects associated with RVS pacing might have resulted from the heterogeneity of the real pacing sites included under the umbrella of RVS pacing concept. These results are in accordance with other studies (Bourke et al, 2002; Dabrowska-Kugacka et al, 2009). Victor et al (Victor et al, 2006) found that in contrast to RVA pacing, RVS pacing preserved LVEF in patients with baseline LVEF ≤45%, but did not gain any advantage of LVEF in patients with baseline LVEF>45%. The absence of significant change in resting LV ejection fraction with both septal and apical pacing in patients with ejection fraction >45% is probably attributable to the time needed for pacing-induced ventricular remodeling in that population. Sweeney et al (Sweeney et al, 2003) showed that in patients with normal LV systolic function without myocardial infarction, the risk of heart failure after RVA pacing was low. So RVA pacing may do little harm to patients with normal LV systolic function and RVOT pacing may have no benefit over RVA pacing for these patients (Cano et al, 2010).

In patients with normal LV systolic function, ventricular synchrony may be of less importance and of more time needed for pacing-induced ventricular remodeling in that population. A longer follow-up, has indeed been able to unveil significant differences in LV volumes and systolic function. The similarity of chronic outcome between pacing in the outflow and the lower septum implies that these sites may be equally useful as more physiological RV pacing sites than the RVA, especially when RV pacing cannot be avoided (Flevari et al, 2009; Rosso et al, 2010).

The PACE study (Yu et al, 2009) showed that the mean left ventricular ejection fraction declined by almost 7 percentage points (from 61.5 ± 6.6 % to 54.8 ± 9.1 %) in the first year of RVA pacing in patients with a normal ejection fraction. Among nine patients in whom the LVEF decreased to less than 45% at 12 months, eight (89%) were in the right ventricular-

pacing group. The authors suggests that the ejection fraction could decrease rapidly in vulnerable patients and that these patients might benefit even more from biventricular pacing (Yu et al, 2009).
Nevertheless, the routine use of LV-based pacing for bradycardia in most patients without heart failure and preserved LVEF is impractical because of the longer procedure time, shorter battery life, higher cost and complications rates, such as lead dislodgement, and less reliability for long-term pacing.

4. Clinical implications and perspectives

This controversy is difficult or impossible to resolve by reviewing the old literature as the techniques for defining septal pacing, using fluoroscopic images in the left anterior oblique position and the tools to reliably direct leads onto the septum have only recently been described (Mond, 2010). the older methods of directing leads onto the septum using a simple curved stylet with torque are not reliable (Balt et al, 2010; McGavigan et al, 2006) and yet comfortably use the term "septal pacing" for many studies, where this was not convincingly demonstrated and the described methods of lead placement would make reliable septal positioning very unlikely. Of importance, there are trials currently underway that may answer the questions posed in this chapter (Kaye et al, 2009).
To address this issue, three randomized prospective multicenter clinical trials are in progress comparing the long-term effects of RV apical versus septal pacing on left ventricular (LV) function Kaye et al, 2009). The three trials are Optimize RV Selective Site Pacing Clinical Trial (Optimize RV), Right Ventricular Apical and High Septal Pacing to Preserve Left Ventricular Function (Protect Pace), and Right Ventricular Apical versus Septal Pacing (RASP). The RV septal lead is positioned in the mid-septum in Optimize RV, the high septum in Protect Pace, and the mid-septal inflow tract in RASP. Lead position is confirmed by fluoroscopy in two planes and adjudicated by a blinded panel. The combined trials will follow approximately 800 patients for up to 3 years. The primary outcome in each trial is LV ejection fraction evaluated by radionuclide ventriculography or echocardiography. Secondary outcomes include echo-based measurements of ventricular/atrial remodeling, 6-minute hall walk distance, brain natriuretic peptide levels, and clinical events (atrial tachyarrhythmias, heart failure, stroke, or death). These selective site ventricular pacing trials should provide evidence of the importance of RV pacing site in the long-term preservation of LV function in patients that require ventricular pacing and help to clarify the optimal RV pacing site.

5. Conclusion

There is actually sufficient evidence that patients with preexisting LV dysfunction and indication for standard "ventricular" pacing should preferentially be treated with resynchronization therapy (CRT) (de Teresa et al, 2007; Höijer et al, 2006). Although biventricular pacing therapy resynchronizes the ventricles of asynchronous hearts, the primary concern during ventricular pacing of otherwise normal hearts is to prevent mechanical desynchronization. It should be highlighted that not all patients develop LV dyssynchrony and newonset heart failure after RV pacing. Therefore, early predictive factors (Zhanget al, 2008; Siu et al,2008 ; Sagar et al, 2010), such as dyssynchrony at the time of implantation, paced QRS width, age, presence of atrial fibrillation, concomitant coronary

artery disease, or compromised LVEF, or antibody status should be further evaluated, they may reveal the patients who are more prone to LV function deterioration and who are consequently better candidates for biventricular pacing. CRT use with milder degrees of LV dysfunction or even normal cardiac function as a means of maintaining cardiac mechanical synchrony is at this date, controversial. The time, cost, and experience required for LV lead placement and the high failure rates due to absent, unsuitable, or unattainable venous anatomy, coupled with eventual operative and postoperative complications, all argue that at the moment, CRT is not the option of choice in patients with conventional indications of pacing, particularly those with preserved LV function.

It is also recognized that the weight of evidence of harm from chronic RV apical pacing is great and that mechanical and safety benefits from RV septal lead positioning for pacing is sufficient in itself to recommend that we now leave the RV apex as a primary implant site (Mond & Vlay, 2010). A septal fixation of the ventricular pacing lead was not associated with increased short- or long-term complications when compared with conventional RVA pacing. In addition, implantation times and fluoroscopy times were shorter in the septal group (Kypta et al, 2008).Coupled to this are the potential physiologic benefits of LV performance that even unproven, cannot be ignored. Therefore, this stimulation site may becomes more and more the default position in different institution although different studies did not reveal a significant outcome benefit. Keeping in mind that there might be at least a subgroup of patients who could do better with septal pacing, the noninferiority of septal pacing could become an argument for a widespread use of this stimulation spot.

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