Review

Focus on right ventricular outflow tract septal pacing

Mise au point sur la stimulation septale infundibulaire

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Summary  Experimental and clinical studies have shown that right ventricular apical pacing may result in long-term deleterious effects on account of its negative impact on left ventricular remodeling through desynchronization. This risk appears more pronounced in patients with even moderate left ventricular dysfunction and generally occurs after at least 1 year of pacing. As right ventricular apical pacing may be associated with the development of organic mitral insufficiency, other sites that allow for more physiological stimulation, such as right ventricular outflow tract septal pacing, have been developed, with good feasibility and reproducibility. However, the prospective randomized studies and meta-analyses to date have only demonstrated a modest effect on ejection fraction in the medium term, without any significant effect on quality of life and morbitmortality. However, the absence of a favorable effect for right ventricular outflow tract septal pacing compared with right ventricular apical pacing in terms of clinical manifestations and patient prognosis appears to be more associated with the designs of these studies, which were not homogeneous with regard to methodology used, judgment criteria, follow-up and, especially, statistical power. Two randomized prospective multicentre studies are currently ongoing in order to evaluate the favorable effect of infundibular septal pacing, when considering the indirect negative effects of right ventricular apical pacing as reported in the literature.

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Abbreviations: AF, atrial fibrillation; CRT, cardiac resynchronization therapy; DDD, dual-chamber pacemakers; EF, ejection fraction; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; RV, right ventricle; RVAP, right ventricular apical pacing; RVOT, right ventricular outflow tract; VVI, single-chamber ventricular pacing.

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Résumé  Les études expérimentales et cliniques ont montré que la stimulation ventriculaire droite apicale peut avoir des effets délétères sur le long terme du fait de son impact négatif sur le remodelage ventriculaire par le biais de la désynchronisation. Ce risque semble plus marqué chez les patients avec dysfonction ventriculaire gauche même modérée et s’exprime généralement après au moins un an de stimulation. Il peut être associé au développement d’une insuffisance mitrale organique. Par conséquent, d’autres sites de stimulation plus physiologique comme la stimulation septale infundibulaire ont été développés avec une excellente faisabilité et reproductibilité. Malheureusement, les études prospectives randomisées et les méta-analyses n’ont jusqu’alors démontré qu’un effet modeste à moyen terme sur la fraction d’éjection sans effet significatif sur la qualité de vie et la morbidité. L’absence d’effet favorable de la stimulation septale infundibulaire par rapport à la stimulation ventriculaire droite apicale sur les manifestations cliniques et le pronostic des patients semble plus liée à la méthodologie des études qui ne sont pas homogènes entre elles en termes de méthodologie, de critère de jugement, de suivi, et surtout de puissance. Deux études prospectives randomisées multicentriques sont en cours qui devraient aboutir très certainement sur un effet favorable de la stimulation septale infundibulaire si l’on se base sur tous les effets indirects négatifs démontrés dans la littérature avec la stimulation ventriculaire droite apicale.

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Why is an alternative to right ventricular apical pacing needed?

Physiopathological consequences of right ventricular apical pacing

The concept of preventing ventricular desynchronization while avoiding stimulation of the RV apex dates back to the middle of the 1990s [1]. Several experimental studies reported that the degree of ventricular dyssynchrony during RV pacing was dependent on several physiological properties of the myocardium: electrical conduction at least four times slower in the myocardium compared with that in the Purkinje system; conduction along muscle fibres twice as fast compared with perpendicular activation, such as during RVAP, when the activation front becomes ellipsoidal, resulting in slowed conduction, particularly in the intermediate and epicardial layers [2]; inability of the electrical impulses in the myocardium to reactivate the Purkinje system, as shown experimentally by Myerburg et al. [3]; a different conduction between the endocardial and epicardial layers on account of the smaller endocardial circumference [4]. All these tissue properties consequently affect the movement of the electrical impulse from the RV to the LV. Several studies have shown that the LV is generally activated at least 50 to 70 ms after the initial RV activation, at 100 ms on average, with a gradual movement from the septum towards the posterior-inferior wall, which is the last area of the LV to be activated [5]. It is thus not surprising that electrical asynchrony is responsible for both inter- and intradyssynchrony in LV myocardial contraction. This asynchrony not only depends on the beginning of the contraction but, more importantly, on the contraction mode, load conditions and fibre orientation in relation to the underlying myocardial state. If the septum is activated first during RVAP, the different phases of contraction will likely depend on interactions with other tissue areas, which are in either the contraction or the relaxation phase [6]. When analysing contraction asynchrony using ultrasound imaging, ‘paradoxical’ septal motion is found, which actually results from various forces exerted in relation to the movement between the RV and LV, thus producing pressure differences across the septum. Several studies have demonstrated that asynchrony has an impact on both systolic and diastolic functions as well as on other phases, particularly isovolumetric relaxation and contraction [7]. Numerous phenomena secondary to inter- and intramyocardial asynchrony develop over time, such as perfusion abnormalities, oxygen demand, histological modifications, localized hypertrophic areas, dilatation of ventricular cavities, occurrence of mitral insufficiency, Filling problems and decreased cardiac output secondary to reduced filling and ejection. Furthermore, the long-term structural consequences are currently known, involving decreased EF and frequent mitral insufficiency [7,8].

Mechanical consequences of RVAP versus septal pacing

The short-term as well as long-term mechanical consequences of permanent apical pacing were evaluated in two recent studies [9,10]. Delgado et al. demonstrated a detrimental acute effect of RVAP on global LV function in 25 healthy patients [9]. A more dyssynchronous LV contraction was observed in the patient group together with an impairment in LV longitudinal shortening and twist, using two-dimensional speckle-tracking strain imaging [9]. The long-term effect was also evaluated in 58 patients with normal LVEF who were prospectively randomized to pacing either from the right ventricular apex or the RVOT septum. After 29±10 months, there was a significant deterioration in LVEF, LV end-systolic volume and left atrial volume, favouring the RVOT septal-paced group [10]. Moreover, the RVAP mode was associated with greater inter- and intramyocardial dyssynchrony than RVOT septal pacing [10].

MOTS CLÉS
Pacemaker ; Défibrillateur ; Stimulation septale ; Stimulation infundibulaire ; Stimulation apicale

Right ventricular outflow tract septal pacing 395
Potential clinical consequences of RVAP

The combination of acute haemodynamic effects and ventricular remodelling explains why electrical and mechanical asynchrony may exhibit adverse clinical consequences in the long-term [8–16]. Several studies showed that RV pacing exerted a negative impact on long-term morbimortality rates compared with atrial pacing, for example, which was preferable in certain indications, such as sinus-node dysfunction [8–16]. Despite the fact that these studies did not compare septal pacing and apical pacing, the detrimental long-term effects of ventricular pacing argue for seeking alternative more physiological pacing sites.

In the main randomized studies involving patients with sinus-node dysfunction but normal LV function, the risk of heart failure and AF was significantly higher during RVAP, showing a deleterious long-term effect compared with preferential atrial pacing, the latter being more physiological [17–23]. Several studies demonstrated a negative correlation between increased percentage of RVAP and long-term cardiovascular events [19]. A subanalysis from the MOST study highlighted the strong risk of AF and hospitalization for heart failure in the two patient groups treated using the DDD (n=707) and VVI (n=632) pacing modes [15]. The risk occurred at a cut-off value of more than 40% for RVAP in the DDD group (HR 2.6; P<0.05) and more than 80% in the VVI group [16]. In the DAVID study, patients with an indication for implantable automatic defibrillator but not for cardiac pacing were randomized into two groups: DDD (heart rate < 70 beats/minute) and VVI (heart rate < 40 beats/minute) [16]. After a median follow-up period of 8.4 months, the percentage of pacing was significantly higher in the DDD group and, moreover, there were more events in relation to the combined endpoint of death and heart failure in this group (HR 1.6; P=0.03). These data imply not only the role of RVAP but also that of elevated heart rate in the occurrence of cardiovascular events [16]. However, the percentage of RVAP cases exhibiting deleterious effects has not been clearly established and the populations most at risk of developing such effects have not been identified, although there appears to be a trend pointing towards patients with underlying conduction problems or coronaropathy [24]. Nonetheless, in daily practice, not all patients benefiting from RVAP will develop LV dysfunction. The risk was estimated at 9% in a retrospective study on 286 patients benefiting from atrioventricular node ablation [25] and at 26% in another retrospective study on 304 patients undergoing definitive cardiac pacing for high-degree atrioventricular block after a follow-up period of 6.5 years [26]. These figures, however, differ from the percentage of ventricular asynchrony reported in numerous studies, estimated at 50% in the acute phase [24]. The potential deleterious effect of RVAP is also shown by interpreting the benefit of CRT in patients with LV dysfunction and cardiac pacemaker [24]. All of the studies demonstrating the benefits of CRT in patients with heart failure and RVAP were reported in a literature review by Tops et al. [24].

However, all these studies concern the deleterious effect of long-term ventricular pacing rather than the consequences of right apical pacing. The studies presented pointed out that one should not pace the ventricle if it is not necessary but there is no clinical evidence yet that these studies will be different with septal pacing. To our knowledge, no clinical studies have been published so far demonstrating a more deleterious clinical long-term effect of RVAP compared with septal pacing.

What are the different pacing modes available as alternatives to RVAP?

The alternatives to RVAP are numerous but not well defined [27–33]: they include His-bundle pacing and para-His pacing, medial septum, lower septum, RVOT in the septal region and, finally, pulmonary infundibulum [28,30]. The most studied area of pacing is RVOT in the septal region (septal RVOT), given the ease of catheter implantation and catheter stability in this region, as well as reproducibility of the method [27–33]. To better comprehend the areas to stimulate at the location termed RVOT, a full understanding of anatomy is necessary [28]. This area was fully described in the recent work of Hillock and Mond [28]. The area of the RVOT includes several parts, with the septum behind, RV free wall in front and a part of the anterior wall (Fig. 1); this area is surrounded by the pulmonary valve above and the tricuspid valve below. Of most interest to us is the septal area: being situated in the lower part of this area is more favourable to physiological pacing, which would not be the case if pacing were done in the upper part of the infundibulum, which is closer to the aorta than the LV. The infundibular region (conus arteriosus) is too high and thin to be an area suitable for pacing. In addition, pacing thresholds are generally increased in this region [28]. Consequently, only the low septal RVOT may be considered a suitable area for pacing; it is situated just below the region known as ‘crista supraventricularis’ and contains trabeculations, which facilitate the implantation of a stimulation catheter [28] (Fig. 1).

In practice, the region being stimulated requires three radioscopic views (Figs. 2–4): the anteroposterior view in order to put the catheter between the RVOT and the middle part of the septum; the left anterior oblique view to differentiate the septal region from the RV free wall, the septal position being characterized by the posterior orientation of the catheter in a column direction in this instance; and the right anterior oblique view, serving to avoid positioning of the catheter at the level of the coronary sinus ostium.

In terms of electrocardiography, the correct positioning of the pacing catheter at the septal level is characterized by a narrower QRS wave compared with other RV areas and, particularly, by a negative or isoelectric vector in D1, whereas it would be positive if the catheter were positioned at the RV level. In precordial derivations, if the septal positioning is correct, broad R waves are recorded from V3 to V6, whereas if the pacing occurs at the RV level, the R waves are negative in V5 to V6 [28]. The implantation technique was previously described, using stylet with posterior angulation [34]. The feasibility of this technique was very good, corresponding to 97% of catheters implanted in this septal infundibular region. Failures occurred in the subgroups of patients exhibiting AF, considerable dilatation of the right cavities or high-grade tricuspid insufficiency [34]. The risk of displacement was the same as with RVAP.
What about scientific evidence in favour of systematic septal pacing?

RVAP was initially chosen on account of its simplicity and low displacement rate, with low pacing thresholds. At the start of the 1980s, the use of screw catheters and other pacing sites, such as RVOT or interventricular septum, were tested in order to reduce the risks of asynchronous pacing. Few studies have evaluated the benefit of a more physiological septal RVOT pacing, with patient numbers that were too low to show the superiority of this technique compared with RV pacing. These studies were combined in 2003 by de Cock et al. in the form of a meta-analysis (Fig. 5) [35]. In this meta-analysis, only two studies demonstrated long-term benefits of RVOT pacing, while the others revealed haemodynamic benefit only in the acute phase [36,37]. The studies varied widely in terms of statistical strength, with populations ranging from 11 to 92 patients [38]. Excluding the study of Giudici et al., comprising 92 patients, the effect demonstrated in the meta-analysis was at the limit of significance [38].

The subgroups benefiting the most from septal RVOT pacing were patients with a lower cardiac output, patients for whom QRS narrowed with pacing and even patients with a low EF and associated coronary heart disease [39,40]. Although septal RVOT pacing is as reliable as RV pacing, numerous limitations were discussed in this meta-analysis, which do not allow the advantages of septal pacing to be categorically determined: the lack of standardization of the pacing site, as only 60% of catheters were actually placed in the infundibular septum in these studies; considerable variability in the evaluation criteria of the studies, with measurements based on isotopic EF, ultrasound, dP/dt or cardiac output; low patient numbers in each study; inclusion of both prospective and retrospective studies; largely insufficient follow-up; monocentric studies [15]. More recently, Bourke et al. compared RVAP and RVOT septal pacing in 20 patients benefiting from atroventricular node ablation for AF, with the results showing that EF was better preserved at 23 weeks when using RVOT septal pacing [41]. A randomized study on the two pacing modes was conducted in 24 patients with complete atrioventricular block requiring permanent pacing, with clear benefit on regional contraction and long-term (18-month) EF shown in favour of RVOT septal pacing [41]. These data thus favour the long-term benefit of RVOT septal pacing compared with RVAP [41,42]. However, debate still continues, notably with the work of Kaye et al. on 103 patients, which did not reveal any difference between the two techniques in terms of improved quality of life in patients with heart failure and AF selected on the basis of LVEF less or equal to 40% [29]. The decisive point in these studies concerns the follow-up period. Studies with a follow-up of several months were generally negative, while those with a follow-up period of more than 12 months showed positive effects. It is therefore clear that the negative remodelling of RVAP occurs over several months (Table 1).

A recently published meta-analysis by Shimony et al. included all of the randomized studies comparing RVAP and non-apical pacing (His, para-His and mid-septal pacing) [43]. A total of 754 patients from 14 studies were analysed, with 385 undergoing ‘septal’ pacing and 369 RVAP. A favourable effect on EF was demonstrated for follow-up periods more than 12 months and for patients with EF less or equal to 45%. In contrast, no significant difference was found in terms of quality of life, functional tests (walking test, maximum oxygen consumption) and morbimortality rates (Fig. 6) [43].

Role of RV lead position in patients in CRT population

The benefit of lateral and basal LV lead position was truly demonstrated in patients who were given a CRT device; on the other hand, only a few studies have studied the role of RV lead position [44–46]. The positioning of the RV catheter at the apex or across the septum in patients undergoing CRT did not appear to exhibit different haemodynamic and
Figure 2. Posteroanterior (PA), 40° right anterior oblique (RAO), left lateral (LL) and 40° left anterior oblique (LAO) fluoroscopic chest images of a dual-chamber pacing system to demonstrate a lead catheter attached to the right ventricular outflow tract septum [28]. Reprinted with permission of Europace.

Table 1 Summary of studies comparing right ventricular apical pacing and other sites of right ventricular pacing.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Pacing site</th>
<th>Evaluation criteria</th>
<th>Follow-up (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victor et al., 1999 [37]</td>
<td>16</td>
<td>RVOT</td>
<td>NYHA; VO₂ max; isotopic EF</td>
<td>3</td>
<td>(−)</td>
</tr>
<tr>
<td>Mera et al., 1999 [36]</td>
<td>12</td>
<td>Septal RVOT</td>
<td>Isotopic EF</td>
<td>2</td>
<td>(+)</td>
</tr>
<tr>
<td>Stambler et al., 2003 [32]</td>
<td>80</td>
<td>RVOT</td>
<td>EF; quality of life; walking test</td>
<td>3</td>
<td>(−)</td>
</tr>
<tr>
<td>Bourke et al., 2002 [41]</td>
<td>20</td>
<td>RVOT</td>
<td>Isotopic EF</td>
<td>4</td>
<td>(−)</td>
</tr>
<tr>
<td>Victor et al., 2006 [55]</td>
<td>28</td>
<td>Septal RVOT</td>
<td>Isotopic EF</td>
<td>3</td>
<td>(−)</td>
</tr>
<tr>
<td>Muto et al., 2007 [56]</td>
<td>233</td>
<td>Mid-RV septum</td>
<td>Ultrasound EF</td>
<td>18</td>
<td>(+)</td>
</tr>
<tr>
<td>Tse et al., 2002 [42]</td>
<td>24</td>
<td>RVOT</td>
<td>Isotopic EF</td>
<td>18</td>
<td>(+)</td>
</tr>
<tr>
<td>Vanerio et al., 2008 [57]</td>
<td>150</td>
<td>RVOT</td>
<td>Mortality</td>
<td>18</td>
<td>(−)</td>
</tr>
<tr>
<td>Kypta et al., 2008 [58]</td>
<td>12</td>
<td>Septal RVOT</td>
<td>Ultrasound EF</td>
<td>18</td>
<td>(+)</td>
</tr>
<tr>
<td>Tse et al., 2009 [59]</td>
<td>12</td>
<td>Septal RVOT</td>
<td>Isotopic EF; walking test</td>
<td>18</td>
<td>(+)</td>
</tr>
<tr>
<td>Flevari et al., 2009 [27]</td>
<td>31</td>
<td>Mid-septum</td>
<td>Ultrasound EF</td>
<td>12</td>
<td>(+)</td>
</tr>
</tbody>
</table>

EF: ejection fraction; NYHA: New York Heart Association; RV: right ventricle; RVOT: right ventricular outflow tract; VO₂: oxygen consumption.
40° Left Anterior Oblique Views

Figure 3. Forty degree left anterior oblique fluoroscopic chest images to demonstrate lead positions in the right ventricle [28]. Reprinted with permission of Europace.

Figure 4. Right anterior oblique (RAO) (40°) and left lateral (LL) anteroposterior oblique views.
From [55], with the authorization of Prof. J. C. Daubert, with courtesy.

clinical effects, as demonstrated recently in a prospective crossover study [47]. To date, the studies studying the role of septal position were either retrospective or too [OK] low powered to demonstrate any significant effect [44,45,47]. These results have been confirmed and emphasized in three randomized studies, including a REVERSE substudy [44—46] (Table 2). The largest study evaluating the RV lead position in patients requiring a CRT was the REVERSE trial substudy

### Table 2  Summary of studies comparing right ventricular apical pacing and right ventricular outflow tract septal pacing in patient populations requiring cardiac resynchronization therapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Follow-up (months)</th>
<th>Effect</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thébault et al., 2012 [46]</td>
<td>346</td>
<td>12.6</td>
<td>NS</td>
<td>Heart failure; mortality; echo data</td>
</tr>
<tr>
<td>Rönn et al., 2011 [47]</td>
<td>33 AF</td>
<td>6</td>
<td>NS</td>
<td>Heart failure; echo data</td>
</tr>
<tr>
<td>Kristiansen et al., 2012 [45]</td>
<td>85</td>
<td>6</td>
<td>NS</td>
<td>Heart failure; echo data</td>
</tr>
<tr>
<td>Khan et al., 2011 [44]</td>
<td>131</td>
<td>6</td>
<td>NS</td>
<td>Heart failure; echo data</td>
</tr>
<tr>
<td>All four studies</td>
<td>595</td>
<td>8</td>
<td>NS</td>
<td>Heart failure; echo data</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; NS: not significant.
Figure 5. Meta-analysis of de Cock et al. [35].

Figure 6. Forest plot comparing the effect of right ventricular apical pacing versus non-apical pacing on left ventricular ejection fraction (LVEF) at the end of follow-up in randomized-controlled trials with mid- and long-term follow-up [43]. ID: identification; WMD: weighted mean difference.
published by Thébault et al. [46]. The position of the RV lead tip was apical in 68.7% and non-apical in 31.3% of patients (n = 346), including the high septum in 4.3%, mid-septum in 24% and free wall in 2.9%. The percentage of worsened patients (study primary endpoint) was not different in this subset of patients with non-apical RV positioning and in patients with RVAP and the echo response variables were also similar (P = 0.16) [46]. Consequently, the retrospective and prospective studies published so far do not support the use of alternate RV stimulation sites for CRT, although this remains to be definitively demonstrated in a randomized prospective study.

**Septal pacing and defibrillation leads**

Concerning defibrillation catheters, given their greater rigidity, it was supposed that the risk of perforation would be less elevated if infundibular septal pacing was conducted without affecting the pacing and defibrillation thresholds, as already discussed [28,48–50]. The only randomized study designed to evaluate the feasibility and performance of RV mid-septal versus apical implantable defibrillator lead placement was recently published by Mabo et al. [50]. The authors demonstrated, in a quite well designed study that included 215 patients, the non-inferiority of the performance of implantable cardioverter-defibrillator leads implanted in the right mid-septum versus the apex position. Septal lead positioning was obtained 89.7% vs. 91.7% in the other group (not significant) and the 1-year rates of related adverse events were similar in both groups as were the percentages of inappropriate therapies (7.9% vs. 7.8%) [50]. All cause mortality was 7.9% in the RV mid-septal group and 2.9% in the RV apical group; the difference was significant in the subset of patients with LVEF less or equal to 30%. Accordingly, no definitive conclusions can be made regarding major adverse events or haemodynamic effects of septal versus apical pacing essentially due to the low pacing rate in both groups [50].

**His-bundle pacing**

Another type of pacing has been the subject of several studies: namely, His-bundle pacing that allows the physiological ventricular activation sequence to be preserved [51–53]. This technique was tested in combination with auriculo-ventricular node ablation in patients with auricular fibrillation with heart failure and narrow QRS [51–53]. Deshmukh et al. also demonstrated that His-bundle pacing was feasible in this subgroup of patients, with an improvement in LV function variables using ultrasound [51–53]. However, a number of limitations were found in this study: the absence of a control group; the almost systematic use of auriculoventricular node ablation (83% of patients permanently implanted); and the feasibility of the technique (78%), with sometimes long and difficult procedures [52]. Despite initially promising results, the feasibility of this technique in practice appears insufficient compared with RVOT septal pacing, despite using a dedicated catheter (4.1 French) developed by Medtronic (Select Secure; Medtronic Inc., Minneapolis, MN, USA) and requiring a catheter guide [28,34]. A recent published study demonstrated that the feasibility of His-bundle pacing in a large population of 133 patients was low (close to 44%) [54].

**Conclusion**

RVOT septal pacing has not yet been proven to provide benefits in randomized studies but indirect data favour its use compared with apical pacing. Several randomized studies are currently ongoing, based on an exact definition of the position of septal pacing by means of radioscopy, using catheters and guides for proper positioning. Three prospective randomized multicentre studies were initiated, although one was stopped due to difficulties in positioning the catheters in the ventricular septum (Optimize RV Selective Site Pacing Clinical Trial). The two other studies are still ongoing, namely the Protect Pate and RASP trials, which are aimed at evaluating RVOT septal pacing compared with RVAP [29].

**Disclosure of interest**

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