Effects of right ventricular pacing on regional myocardial glucose metabolism

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KEYWORDS
right ventricular pacing; myocardial glucose metabolism; myocardial blood flow; positron emission tomography

Abstract Aims Permanent right ventricular apical pacing (RVP) is associated with a wide range of myocardial abnormalities. The purpose of this study was to determine the changes over time of RVP on myocardial blood flow (MBF) and glucose metabolism as assessed by positron emission tomography (PET).

Methods In eight candidates for permanent pacemaker implantation PET imaging was performed with 13N-ammonia and 18F-Fluorodeoxyglucose (FDG) to assess MBF and glucose metabolism before (PET1) and repeated after 3 months of RVP (PET2). For the analysis, the left ventricle was divided into three parts (apex, mid-ventricular and base) and subdivided into six segments (inferior, posterior, lateral, anterior, antero-septal and infero-septal).

Results After RVP, defects of FDG uptake were found in the left ventricle near the stimulation site, without corresponding changes in MBF. Changes over time in the mean FDG uptake were statistically significant between PET1 and PET2 in the apical inferior, apical-posterior, apical-anterior, apical antero-septal, apical infero-septal, mid-inferior and mid-infero-septal segments.

Conclusions This study shows that RVP induces major changes in the distribution of FDG uptake in the left ventricular myocardium. FDG uptake significantly decreases in the regions surrounding the pacing site.

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Right ventricular apical pacing (RVP) is associated with a wide range of functional myocardial abnormalities [1-4]. Moreover, recent studies [5-8] have shown that unnecessary pacing can lead to an increased incidence of hospitalization for heart failure and should be avoided. Although the mechanical and haemodynamic consequences of the abnormal ventricular activation have been well characterized, little is known about the long-term effects on myocardial blood flow (MBF) and glucose metabolism.

The value of positron emission tomography (PET) in the diagnosis of myocardial viability is firmly established, but the potential effect of RVP on regional MBF and glucose metabolism may complicate the interpretation of PET data as has been demonstrated with single-photon emission computed analysis (SPECT) evaluation of these patients. Indeed numerous SPECT studies [1,4,9,10] have demonstrated that RVP results in perfusion defects in regions surrounding the pacing site. In addition, ventricular pacing has been shown to cause reduced blood flow, glucose uptake, and workload over the stimulation site in canine hearts [11,12], and reduced inferior and septal blood flow in patients [13].

Accordingly, the purpose of this study was to determine the changes over time of permanent RVP on regional myocardial glucose metabolism and MBF as assessed by PET.

Methods

Patients and pacemakers

We performed PET studies in eight patients with bradyarrhythmia who were candidates for permanent pacemaker implantation. All patients gave informed consent to participate in the study and underwent a first PET study (PET1) a few days (mean 1 day, range 0-3 days) before their pacemaker implantation. In the late post-operative period (mean 120 days, range 64-310 days post-implantation), all patients underwent a second PET examination (PET2) to assess the changes induced by the RVP.

Patient characteristics are summarized in Table 1. Four patients had coronary artery disease and two of them had had a myocardial infarction in the past. No patients had left bundle branch block (LBBB) or presented symptoms or clinical signs of unstable coronary artery disease and no significant clinical event occurred during the study period.

The same surgeon performed all pacemaker implantations, following current guidelines. Ventricular electrode placement was performed under fluoroscopy to ensure appropriate positioning at the apex of the right ventricle, which is currently the site of choice for ventricular stimulation.

Pacemakers were programmed in DDD mode with a physiological rate-adaptive AV-delay to ensure stable ventricular pacing. Only patients in whom complete ventricular pacing was achievable were included. To check this criterion, several tests were performed systematically. Pacemakers were temporarily programmed in asynchronous ventricular mode (VOO) to ensure complete capture of the ventricle by the pacemaker and the paced-QRS width was measured. This width was compared with the paced-QRS width under usual programmed conditions (dual-chamber pacing mode DDD in all patients), to ensure less than 10% disparity between the two measurements. Complete pacemaker evaluation was performed before discharge, at 6 weeks, and every 3 months after pacemaker implantation. During these evaluations, complete testing of the stimulation system was performed; a pacemaker diagnostic function analysis was also performed to ensure a ventricular capture rate of >95%.

Pet image acquisition

Myocardial perfusion was assessed with 13N-ammonia (NH₃) and glucose metabolism with 18F-Fluorodeoxyglucose (FDG). Imaging was performed as previously described [14] with a PET scanner (ECAT 931, CTI Siemens, Knoxville, TN, USA) that simultaneously provides 15 transaxial images over a 10.5-cm field of view (intrinsic resolution: ±6 mm FWHM). A 2-min rectilinear scan was performed to ensure optimal patient positioning in the tomograph. A 10-min transmission scan was
obtained to correct for photon attenuation. An intravenous bolus of NH₃ (10 mCi) was then administered over 30 s. Acquisition of serial transaxial emission images was started simultaneous to the injection of NH₃. Dynamic image sequence consisted of 12 10-s frames, followed by four 30-s frames and one 360-s frame. One hour later, after physical decay of the NH₃ activity to near undetectable levels, an FDG scan was carried out. Ten mCi of FDG was injected and followed by an emission scan of 20 min. Cardiac medications were discontinued at least 24 h before the PET study. All patients were studied after an overnight fast. To standardize the dietary state and enhance the myocardial glucose uptake, the patient received 50 g of oral glucose 40 min before the start of the FDG-PET. Heart rate, systemic blood pressure (cuff measurements), and 12-lead electrocardiograms were recorded throughout the PET study.

Image analysis and myocardial blood flow determination

The images were reconstructed using a Hann filter with a 0.5 cut-off frequency and analyzed after filtered back-projection. Tomographic data were quantified as previously described[15,16]. Briefly, NH₃ and FDG cross-sectional images were analyzed with an operator-interactive computer programme using circumferential profiles. The programme normalized FDG and NH₃ counts within a given myocardial cross-section to maximal activity in the same ventricular slice. The alignment axis of the left ventricle for creation of the vertical and short axis was determined by an experienced operator on the last frame of the NH₃ dynamic sequence, displaying the best tissue-to-blood ratio. The axis values were used to repeat determination on FDG images and for the second PET examination for each patient. The left ventricular wall was divided into three parts: basal, middle, and apical. Each part was subdivided into six segments: inferior, posterior, lateral, anterior, antero-septal and infero-septal. Further analyses were thus performed on 18 segments.

Regional MBF was quantified using a previously validated three-compartment model [17]. A 3-point semi-quantitative score was applied to both FDG and NH₃ images: normal uptake (>75%) was scored two, a moderate defect (uptake 50–75%) was scored one, and a severe defect (uptake < 50%) was scored zero [18]. To evaluate the relationship between myocardial perfusion and glucose metabolism on each PET study for each segment, a ratio was calculated by dividing the FDG-score by the NH₃-score.

Statistical analysis

The null hypothesis of no significant effect of cardiac pacing on myocardial metabolism was tested in 18 regions of the left ventricle using repeated-measures ANOVA. We used $P < 0.05$ as the significance level for overall analysis but adjusted the level of significance for multiple comparisons using the Bonferroni correction. Because we considered 18 pair comparisons (Fig. 1), the level of significance for each was $P < 0.05/18 = 0.0028$.

Results

Haemodynamic data

These data are summarized in Table 2. Non-significant differences for haemodynamic parameters were found for heart rate although patients

![Graph showing regional distribution of glucose metabolism](https://academic.oup.com/europace/article/7/6/584/545565/586N.Preumont et al.)}
presented with a lower rate for the first PET study (PET1: heart rate $Z_{57}$ 57 G 16 bpm; PET2: heart rate $Z_{69}$ 69 G 9 bpm). Heart rate variability was reduced by pacemaker stimulation for the second PET study. There was a trend to a higher systolic blood pressure during PET1 (151 G 24 mmHg vs 135 G 19 mmHg, $P = 0.12$).

### NH$_3$ uptake

Within each set of scans (PET1 and PET2) there was a statistically significant heterogeneity of NH$_3$ uptake characterized by lower values in the apical region (ANOVA for repeated measures, $P < 0.0001$), which did not differ between PET1 and PET2. There was no statistically significant difference between this regional distribution of NH$_3$ uptake in PET1 and PET2.

### Myocardial blood flow

Mean absolute MBF (ml/min/100 g) values were not statistically different between PET1 and PET2 ($74 \pm 2$ vs $85 \pm 2$ ml/min/100 g). The regional distribution of MBF was unaffected by cardiac pacing. There was no difference at $P < 0.01$ between PET1 and PET2 for any segment, even if no correction for multiple comparisons was made.

### FDG uptake

There was heterogeneous FDG uptake in the left ventricular wall on both PET studies (ANOVA, $P < 0.0001$, Fig. 1). In contrast to NH$_3$ data, the heterogeneous distribution of FDG uptake was statistically different between PET1 and PET2 (ANOVA, $P < 0.0001$). This difference was related to a lower uptake in some apical and middle septal segments. A corrected paired $t$-test showed significant differences in the apical inferior (75.9 $\pm$ 8.2 vs 63.1 $\pm$ 12.1%), apical-posterior (70.9 $\pm$ 7.5 vs 47.7 $\pm$ 11.1%), apical-anterior (78.5 $\pm$ 8.3 vs 59.2 $\pm$ 15.6%), apical antero-septal, apical infero-septal (76.3 $\pm$ 7.2 vs 48.1 $\pm$ 14.3%), mid-inferior (77.7 $\pm$ 8.3 vs 50.4 $\pm$ 13.2%) and mid-infemo-septal (86.2 $\pm$ 8.1 vs 58.6 $\pm$ 15.9%) segments (Fig. 1). In patients with previous defects due to myocardial infarction, no major changes over time were observed for segments remote from the region affected by pacing. Fig. 2 illustrates the changes in FDG uptake over time in one patient.

### FDG–NH$_3$ relationship

The ratio of FDG to NH$_3$ uptake was homogeneously distributed on PET1. On PET2 the distribution of the ratio was similar to that of FDG uptake, and was significantly heterogeneous (ANOVA, $P < 0.0001$). A corrected paired $t$-test showed significant differences in the apical inferior, apical lateral, apical antero-septal, and apical infero-septal distributions.

### Semi-quantitative score

To illustrate the regional discordance between myocardial perfusion and glucose metabolism (reverse mismatch), the semi-quantitative score of the PET2 study was subtracted from that of the PET1 study for each segment. Fig. 3 illustrates the values of this subtracted score in each segment, summed over all patients. Regional discordance appeared mainly in the apical and the infero-septal regions. However, in some patients, a reverse mismatch was also found in the antero-septal, the inferior, or the posterior parts of the left ventricle.

### Discussion

This study demonstrates that RVP drastically modifies myocardial metabolism and the distribution of FDG uptake in the left ventricular myocardium. Interestingly, this metabolic remodelling occurred in a controlled and “iatrogenic” situation.

RVP is associated with a wide range of functional, perfusion, metabolic and histological myocardial

### Table 2 Haemodynamic measurements

<table>
<thead>
<tr>
<th></th>
<th>PET1</th>
<th>PET2</th>
<th>$P$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>57 (16)</td>
<td>69 (9)</td>
<td>0.18</td>
</tr>
<tr>
<td>BP, Systolic (mmHg)</td>
<td>151 (24)</td>
<td>135 (19)</td>
<td>0.12</td>
</tr>
<tr>
<td>BP, Mean (mmHg)</td>
<td>101 (10)</td>
<td>94 (7)</td>
<td>0.14</td>
</tr>
<tr>
<td>BP, Diastolic (mmHg)</td>
<td>74 (9)</td>
<td>77 (5)</td>
<td>0.44</td>
</tr>
<tr>
<td>Rate-pressure product</td>
<td>8587 (2294)</td>
<td>9431 (2040)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± standard deviation. PET1 = Before right ventricular pacing; PET2 = after right ventricular pacing; HR = heart rate; BP = blood pressure; bpm = beats per minute.
abnormalities. According to previous studies, long-term RVP is associated with impairment of myocardial function with a significant negative inotropic effect, impaired global left ventricular function and wall motion abnormalities [1,2]. Thus, in patients with normal ventricular function and intact AV-conduction, haemodynamic parameters are worse with atrial triggered RVP than with ventricular activation through the native conduction system. It is now well established that pacing the right ventricle may alter the heart in a negative way [6].

The effects on MBF in such patients are less known and have been studied mainly by thallium-201 SPECT [1,2,9,10]. These previous studies have shown that patients with pacemakers and without coronary artery disease show perfusion defects in infero-posterior and apical regions. Myocardial perfusion defects were common and increased with the duration of pacing [2]. Furthermore, those patients who continued to be paced during exercise had a high incidence of false positive thallium-201 SPECT defects [9]. Alterations in coronary flow velocities and in coronary flow reserve have been described and may be at least partially responsible for the uncertain specificity of dipyridamole myocardial perfusion scintigraphy [10]. Experimental studies in paced animal models have also demonstrated reduced regional blood flow with pacing compared to that obtained with normal sinus rhythm [11].

Figure 2  Short axis reconstructions of cardiac FDG-PET acquisition are shown from left to right: in the apex, the mid-ventricular portion and the base of the left ventricle; before (top) and 3 months after right ventricular pacing (bottom). The second FDG scan demonstrated, after right ventricular pacing, a large fixed area of poor FDG uptake in the apex and in the mid inferior, mid-infero-septal and mid-antero-septal segments.

Figure 3  Polar map of the appearance of regional discordance between myocardial perfusion and glucose metabolism after right ventricular pacing. The summed value of the FDG- to NH₄⁺-score ratio over the eight patients is displayed on a five-level grey scale.
flow within the interventricular septum [11]. Nielsen et al. randomized patients with sick sinus syndrome to either DDD or AAI pacing for 2 years and their MBF was quantified using NH3 PET scanning [13]. These authors showed that chronic DDD pacing reduced inferior, septal and global mean MBF compared with temporary AAI pacing. In our study, the effect of right ventricular pacing on MBF appears to be less important, without significant changes over time. However, it is difficult to clarify this effect in our population. Indeed, some patients had coronary artery disease and previous myocardial infarction. Hence, further investigations should be conducted on a larger group of patients (with and without CAD) to elucidate the possible interactions of RVP and MBF changes in relation to the presence of cardiac disease. Furthermore, the quantification of absolute MBF must take into account the haemodynamic conditions of the measurement [19]. Normalization of the MBF may partly deal with this limitation but raises other methodological issues. Some patients presented with bradycardia during PET1, and the heart rate was corrected by pacemaker stimulation during PET2.

Previous studies have shown an association between abnormal ventricular activation and, also, other metabolic abnormalities [1]. LBBB results in decreased septal FDG uptake unrelated to perfusion reduction [8]. This "reverse mismatch" has also been evaluated with other tracers [20-22]. Ono et al. [11] studied regional myocardial perfusion and glucose metabolism in experimental LBBB which was induced by apical right ventricular pacing in an animal model. The abnormal activation resulted in reduced myocardial perfusion and glucose uptake in the septum because of impaired systolic thickening and raised intramyocardial pressure in the septum. Our study demonstrated important metabolic abnormalities induced by RVP in the left ventricular myocardium. Heterogeneous regional distribution of both NH3 and FDG were noted in PET1. This is probably due, in part, to a volume effect in the apical region, which is thinner than the middle and basal regions. These metabolic abnormalities appeared to be unrelated to perfusion impairment. Indeed, the regional distribution of the FDG/NH3 ratio was actually homogeneous throughout the left ventricular wall on PET1. The defects in FDG uptake, observed after cardiac pacing, were present in the apical inferior, apical-posterior, apical-anterior, apical antero-septal, apical infero-septal, mid-inferior, and mid-infero-septal segments, near the right apical stimulation site (Fig. 1). This unusual pattern of decreased FDG uptake despite relatively preserved MBF has already been described as a "reverse mismatch" in LBBB [18] as well as in patients with dilated cardiomyopathy [23].

However, the pathophysiological mechanism of reduced glucose utilization despite normal perfusion remains unclear. After glucose loading, FDG uptake is increased in normal myocardium where it maintains a distribution similar to the perfusion [24]. Uptake of FDG by the myocardium depends on many factors such as dietary state, cardiac workload, response of the tissue to insulin, sympathetic drive, and the presence and severity of ischaemia [25]. As underlined elsewhere, FDG uptake in the myocardium represents a metabolic signal that can be affected globally by the metabolic state of the patient and regionally by alterations in substrate use [26]. In the light of our study, it appears that exogenous electrical stimulation may induce changes over time in regional metabolic pathways leading to decreased myocardial FDG uptake. An animal study [27] has demonstrated that, during RVP, regions surrounding the pacing site are hypofunctional. Indeed, this experimental study, using magnetic resonance imaging tagging, showed that the spatial distribution of myofibre shortening and work was considerably modified by asynchronous electrical activation. According to the authors [27], these abnormalities appear large enough to consider local myocardial function as an important determinant for abnormalities in perfusion, metabolism, structure and pump function during RVP. These findings are in line with PET studies on the relationship between myocardial efficiency and oxidative metabolism with cardiac resynchronization therapy [28,29].

Furthermore, another study [30] has shown that RVP also disturbs the adrenergic innervation of the left ventricle, as assessed by I123-MIBG scintigraphy. Interestingly, these regional disturbances affect mainly the inferior and the apical walls, which in our study also exhibited abnormal glucose metabolism. These regional changes may represent the metabolic correlate of persistent cellular modifications that result from ventricular pacing [31].

Following RVP, other studies have shown altered cardiac histological features in the myocardial wall over the activation site [32,33]. One study [1] detected no abnormal light or electron microscopic findings on subjects paced for a shorter period of time. We identified metabolic changes early after introduction of chronic pacing. A longer period of chronic pacing may be required for structural changes to be demonstrated by histological methods.

Although the value of PET FDG/NH3 study in the diagnosis of myocardial viability is firmly established, no data are available for patients with
Implanted pacemakers. Regions which show a concordant reduction in both MBF and FDG uptake ("flow-metabolism match") are labelled as predominantly infarcted, whereas regions in which FDG uptake is relatively preserved or increased despite having a perfusion defect ("flow-metabolism mismatch") are considered to represent jeopardized viable myocardium [25]. In the light of our study, RVP appears to cause a decrease in FDG uptake despite relatively preserved MBF in the regions surrounding the pacing site, causing a reverse mismatch. Thus, our study suggests that there is a risk that the necrotic area may be overestimated by FDG-PET in patients with a right ventricular pacemaker.

Conclusions

The results of this study show that the effects of RVP on regional myocardial glucose metabolism are prominent in the regions surrounding the pacing site, which exhibit a significant reduction in FDG uptake. These data point to profound metabolic regional changes induced by RVP, mainly in the apex and in the mid-infero-septal area.

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