Regional Myocardial Blood Flow in Patients With Sick Sinus Syndrome Randomized to Long-Term Single Chamber Atrial or Dual Chamber Pacing—Effect of Pacing Mode and Rate

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OBJECTIVES

This study aimed to evaluate regional myocardial blood flow (MBF) and global left ventricular ejection fraction (LVEF) during chronic pacing in patients with sick sinus syndrome (SSS) randomized to either single chamber atrial (AAI) or dual chamber (DDD) pacing.

BACKGROUND

Experimental studies indicate that chronic pacing in the right ventricular apex changes regional MBF, thereby compromising left ventricular function.

METHODS

Thirty patients (age 74 ± 10 years) were randomized to AAI (n = 15) or DDD (n = 15) pacemakers. After 22 ± 7 months of pacing, MBF was quantified with 13N-labeled ammonia positron emission tomography scanning at 60 beats per min and 90 beats per min. Patients in the DDD group furthermore underwent MBF measurement at temporary AAI pacing, 60 beats per min. Myocardial blood flow was assessed in the anterior, lateral, inferior and septal regions, and the global mean MBF was calculated. Left ventricular ejection fraction was determined by echocardiography at pacemaker implantation and at the time of MBF measurements.

RESULTS

Myocardial blood flow at rates 60 and 90 beats per min did not differ between the AAI and DDD groups. During temporary AAI pacing in the DDD group, MBF was significantly higher than during DDD pacing in both the inferior (p = 0.001) and septal (p = 0.004) regions and also globally (0.61 ± 0.15 vs. 0.53 ± 0.13 mL/g · min⁻¹, p = 0.005). In the DDD group, LVEF decreased from pacemaker implantation to time of MBF measurements (0.61 ± 0.09 vs. 0.56 ± 0.07, p = 0.013). Left ventricular ejection fraction during temporary AAI pacing at time of MBF measurements was not different from LVEF at pacemaker implantation.

CONCLUSIONS

In patients with SSS, chronic DDD pacing reduced inferior, septal and global mean MBF as well as LVEF, as compared with temporary AAI pacing. The LVEF reversed to baseline level during temporary AAI pacing despite 22 months of permanent ventricular pacing preceding it. Augmenting pace rate to 90 beats per min increased MBF equally in the two treatment groups. (J Am Coll Cardiol 2000;35:1453–61) © 2000 by the American College of Cardiology

Patients with the sick sinus syndrome (SSS) and normal atrioventricular (AV) conduction can be treated with single chamber atrial (AAI) or dual chamber (DDD) pacemakers, whereas single chamber ventricular pacing (VVI) should be avoided (1,2). The advantage of DDD pacing is that it protects against bradycardia in the few patients (less than 1% per year) (3,4) who subsequently develop high degree AV block. However, the hemodynamic disadvantage of DDD pacing is that the electrical stimulation in the right ventricular apex causes an asynchronous ventricular activation, contraction and relaxation pattern, which reduces systolic and diastolic ventricular function (5–7). In contrast, the hemodynamic advantage of AAI pacing is that the normal physiological ventricular activation and contraction pattern is preserved and unaffected by the pacemaker stimuli. Both experimental and clinical studies have indicated
that chronic pacing in the apex of the right ventricle might be detrimental to the left ventricular function (2,8–10). The mechanisms behind this detrimental effect are unknown, but some studies have indicated that a reduced regional myocardial blood flow (MBF) may play a role (8,9,11,12). However, the regional MBF during chronic pacing has never been assessed quantitatively in human studies.

The aim of this study was to evaluate global and regional MBF during chronic pacing in patients with SSS randomized to AAI or DDD pacing using $^{13}$N-labeled ammonia positron emission tomography (PET) imaging and to study whether pacing-induced changes in MBF are associated with alterations in global left ventricular function.

**METHODS**

**Study population.** Patients included in this study were recruited from an ongoing prospective randomized trial of rate responsive AAI (AAIR) versus DDD (DDDR) pacing, which since 1994 has been enrolling consecutive patients with SSS, normal AV conduction and no bundle branch block at our institution (13). After giving informed consent, patients are randomized in the parent study to one of three treatments: AAI pacemaker, DDD pacemaker programmed with a physiological, rate-adaptive AV delay (110–150 ms) and DDD pacemaker programmed with a fixed long AV delay (≥250 ms). The main end points in the parent study are changes in left ventricular size and ejection fraction and in left atrial size measured by echocardiography. All patients randomized to and treated with either 1) an AAI pacemaker or 2) a DDD pacemaker programmed with a physiological AV delay (110–150 ms) in the parent trial and who have been followed for at least one year after implantation were considered candidates for this study. A total of 69 consecutive patients fulfilled these criteria. Ten of the patients were excluded because of permanent (n = 3) or acute (n = 1) atrial fibrillation or concurrent severe noncardiac illness (n = 6). Twenty-eight patients were not willing to participate in this study, and one patient was not able to undergo the MBF study due to claustrophobia. Therefore, 30 patients were included in this study, 15 with AAI pacemakers and 15 with DDD pacemakers. Patients excluded or unwilling to participate did not differ from patients included regarding age, sex, New York Heart Association functional class or LVEF. Patients with prior myocardial infarction or angina pectoris were classified as having coronary artery disease. All patients refrained from consuming caffeine-containing beverages or food for ≥24 h, and smokers refrained from smoking for ≥4 h before the study (14,15). A time line diagram of measurements made in this study is shown in Figure 1.

**Pacemakers, pacemaker leads and pacemaker programming.** Standard rate-adaptive single chamber pacemakers and dual chamber pacemakers were used. All atrial leads were implanted in the upper parts of the right atrial free wall. In the AAI group, nine patients had unipolar leads and six had bipolar leads, thirteen had leads with active fixation. In the DDD group, six patients had unipolar leads and nine had bipolar leads in the right atrium; 14 of these leads were actively fixated. All patients with DDD pacemakers had unipolar leads with passive fixation implanted in the right ventricular apex. The rate response function was active in all but one patient with an AAI pacemaker. Lower and upper rates were programmed individually. In the DDD group, the paced AV delay was individually programmed to a length, which ensured ventricular capture in the resting electrocardiogram (ECG) (AV delay: 110/130/140/150 ms in 1/3/2/9 patients), and rate-adaptive AV delay was activated. The number of sensed and paced events during the period from pacemaker implantation to determination of MBF was retrieved from the pacemaker event counters (Fig. 1).

**PET and quantification MBF.** Myocardial blood flow was quantified using $^{13}$N-labeled ammonia and dynamic PET imaging (Model EXACT HR 961, Siemens/CTI, Knox-
ville, Tennessee). A 20 min attenuation scan was performed first to correct for photon attenuation. The image acquisition (12 frames of 10 s each) started simultaneously with the intravenous injection of $^{13}$N-labeled ammonia (740 MBq in 20 ml saline; 30 s bolus injection). After this dynamic sequence, two 30-s, one 60-s and one 900-s static nongated image frames were acquired to obtain high resolution images for the assignment of regions of interest. The transaxially acquired images were reoriented to obtain 12 short-axis images of the left ventricle as described previously (16). Three midventricular short-axis planes of the static images were selected to assign four regions of interest (ROIs) referring to the three major coronary vascular territories (anterior: left anterior descending artery [LAD], lateral: left circumflex artery [LCX] and inferior right coronary artery [RCA]) and the interventricular septum. The ROIs were subsequently copied to the dynamic image sequence. This allowed us to obtain myocardial tissue time activity curves for $^{13}$N-labeled ammonia (17). The arterial input function was obtained from a small ROI in the center of the left ventricular blood pool on the static frame and copying this ROI to the serially acquired blood pool images (18). The myocardial time-activity curves were corrected for partial volume effects by assuming a uniform left ventricular wall thickness of 1 cm, which yields a recovery coefficient of 0.73 (19). Corrections were also made for physical decay of $^{13}$N-labeled ammonia activity on both the blood pool and myocardial time-activity curves. Myocardial blood flow was quantified by fitting the corrected tissue and blood pool time-activity curves to a validated two compartment model for $^{13}$N-labeled ammonia (16). This model corrects for spillover activity from the left ventricular blood pool to the left ventricular myocardium (19,20). Myocardial blood flow was calculated in each ROI. The global mean MBF was calculated as the average MBF in the four ROIs. In patients with prior myocardial infarction, regions with scar were avoided when defining ROIs for obtaining time activity curves as described by Czermin et al. (21). Resting MBF is closely related to rate-pressure product (RPP), defined as systolic blood pressure $\cdot$ heart rate (17), and, therefore, MBF values normalized to the RPP were also calculated (corrected MBF = [MBF/RPP] $\cdot$ 10.000).

**Study protocol.** In all patients, MBF was measured twice during their respective pacing modes; one measurement in which the pacemaker was programmed with the patient’s usual lower rate (MBF-60) and one during temporary increase of the pacing rate to 90 beats per min (MBF-90), corresponding to the heart rate during normal daily activities in these patients. Patients in the DDD group underwent a third MBF measurement after reprogramming of the pacing mode to AAI pacing and usual lower rate (MBF [DDD→AAI]-60). All MBF measurements were performed in the same scanning session on one day in each patient. In all cases, MBF-60 was measured first to obtain MBF during chronic pacing without any possible disturbing effect of the temporary changes in pacing mode or rate. In the DDD group, the order of the two additional measurements was randomized. Alterations in pacing rate and mode was done 5 min before injection of $^{13}$N-labeled ammonia and reverted to the usual lower rate and usual mode after completion of the dynamic image acquisition (120 s after start of the $^{13}$N-labeled ammonia infusion). The first MBF study was performed after each patient had rested in the supine position for at least 30 min. The 12-lead ECG was monitored continuously throughout each study. Heart rate and blood pressure were measured twice immediately after each $^{13}$N-labeled ammonia injection with an automatic blood pressure device. The average value of these two measurements is reported.

**Echocardiography.** At pacemaker implantation and again within two months of the MBF studies (Fig. 1), two-dimensional and M-mode echocardiography was done in all patients. In patients with DDD pacemaker, echocardiography at the time of MBF measurement was done both during DDD pacing and during temporary AAI pacing. Left ventricular two- and four-chamber apical views were obtained; left ventricular end-diastolic and end-systolic volumes were computed using the biplane (or uniplane if only one of the apical views was available) modified Simpson’s method (22), and LVEF was calculated. Left ventricular end-diastolic and end-systolic diameters were measured on M-mode echocardiograms obtained from the parasternal window using the leading edge technique (23). All echo-cardiograms were made and analyzed by the same investigator (J.C.N.). Analysis of the echocardiograms was done unblinded with regard to pacing mode, but echocardiograms obtained at time of PET scanning were analyzed without knowledge of the results of baseline echocardiograms. In a repeatability study of LVEF measurements using the modified Simpson’s technique on 10 consecutive patients, the mean and standard deviation of the intraindividual differences in LVEF were 0.01 and 0.04, respectively.

**Ethics.** The study was approved by the National Danish Ethical Committee and was conducted in accordance with the Helsinki declaration. Each patient gave written, informed consent.

**Statistical analysis.** Based upon an expected standard deviation (SD) in baseline MBF of 0.1 mLg$^{-1}$·min$^{-1}$, a minimum clinically important difference in MBF of 15% between the two treatment groups (mean MBF expected to be 0.7 mLg$^{-1}$·min$^{-1}$), alpha $=$ 0.05 and a power (1-beta) of 0.8, the number of patients necessary in each group was calculated to 15.

Continuous variables are reported as mean ± SD. The unpaired $t$ test or the nonparametric Mann-Whitney $U$ test was utilized to compare blood flow, hemodynamic measurements and echocardiographic findings between the two treatment groups. The paired $t$ test or the nonparametric Wilcoxon signed rank test was utilized to compare
parameters within each treatment group. Chi-square test was used to compare categorical variables. SPSS 8.0 for windows was used for statistics. All probability values are two-tailed; p < 0.05 was considered statistically significant.

RESULTS

Baseline parameters of the study population were similar in the two groups (Table 1). In two patients in the AAI group, increase of the heart rate to 90 beats/min was not possible. In one patient, atrial fibrillation was elicited by rate increase, and, in the other patient, inhibition of the atrial channel by accessory retrograde atrial activation occurred during increased rate. Myocardial blood flow-60, therefore, was determined in 30 patients, MBF-90 in 28 patients (13 in the AAI group) and MBF (DDD→AAI)-60 in all 15 patients in the DDD group. Myocardial blood flow (DDD→AAI)-60 was measured before MBF-90 in eight patients in the DDD group.

Hemodynamics. Blood pressures and RPP were similar in the two treatment groups when measured at pacing rate 60 beats/min (Table 2), while RPP was significantly higher at pacing rate 90 beats per min in both groups (p < 0.0005). In the AAI group, both the systolic and diastolic blood pressure were significantly higher at pacing rate 90 beats per min than at pacing rate 60 beats/min (p = 0.001). In the DDD group, the diastolic blood pressure was significantly higher at pacing rate 90 beats/min than at pacing rate 60 beats/min (p = 0.007), whereas the systolic blood pressure did not change (Table 2). In the DDD group, there were no differences in blood pressures or RPP between DDD pacing mode and temporary AAI pacing mode, rate 60 beats/min.

MBF measurements. Global mean MBF-60 did not differ between the AAI and DDD groups (Fig. 2, Table 2). Nor did MBF-60 measured in each of the four regions differ statistically significant between the two treatment groups although there was a tendency towards lower MBF in the DDD group in all four regions (Table 2). Global mean MBF-90 was not different between the AAI and DDD groups (Fig. 2, Table 2). In both the AAI and the DDD groups, MBF-90 were higher than MBF-60 (p < 0.0005) in all four regions (Fig. 3, Table 2).

In the DDD group, global mean MBF (DDD→AAI)-60 was significantly higher than global mean MBF-60 (p = 0.005) (Fig. 2, Table 2). Analyzing each region separately, MBF (DDD→AAI)-60 was higher than MBF-60 in all four regions, but the difference was significant only in the RCA (p = 0.001) and septal (p = 0.004) regions (Fig. 3, Table 2).

After correction for RPP, global mean MBF-60 re-

### Table 1. Patient Characteristics at Time of MBF

<table>
<thead>
<tr>
<th></th>
<th>AAI</th>
<th>DDD</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>71 ± 12</td>
<td>76 ± 9</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>4/11</td>
<td>9/6</td>
</tr>
<tr>
<td>Time since pacemaker implant (months)</td>
<td>23 ± 7</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>Brady-tachy syndrome at implant</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4</td>
<td>6</td>
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<tr>
<td>Prior MI</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV</td>
<td>10/4/1/0</td>
<td>11/4/0/0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Smoker</td>
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<td>Medication</td>
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<tr>
<td>Beta-blocker</td>
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<td>5</td>
</tr>
<tr>
<td>Ca-blocker</td>
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<td>3</td>
</tr>
<tr>
<td>ACE inhibitor</td>
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<td>Digoxin</td>
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<td>6</td>
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<tr>
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<td>12</td>
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<tr>
<td>Anticoagulation</td>
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<td>2</td>
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<td>Diuretics</td>
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<td>7</td>
</tr>
<tr>
<td>Programmed pacemaker rate</td>
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</tr>
<tr>
<td>Lower rate 50/60/70/75 beats/min</td>
<td>4/7/4/0</td>
<td>2/11/1/1</td>
</tr>
<tr>
<td>Upper rate 120/130 beats/min</td>
<td>11/3</td>
<td>14/1</td>
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</table>

Figures indicate number of patients. Continuous data are presented as mean ± SD. Brady-tachy syndrome at implant is defined as at least one episode of documented supraventricular tachycardia before pacemaker implantation.

AAI = single chamber atrial pacemaker; ACE = angiotensin-converting enzyme; DDD = dual chamber pacemaker; MBF = myocardial blood flow; MI = myocardial infarction; NYHA = New York Heart Association heart failure classification.
remained similar in the two groups (DDD group 0.68 ± 0.15 vs. AAI group 0.79 ± 0.19, p = 0.08). However, in the RCA region, MBF-60 was significantly lower in the DDD group than it was in the AAI group (0.63 ± 0.18 vs. 0.83 ± 0.24, p = 0.02). Myocardial blood flow-90 was not different between treatment groups, globally or in any of the four regions. When pacing mode was changed from DDD to AAI in the DDD group, both the global mean MBF and the regional MBF changed in the same manner as before correction for RPP.

Echocardiography. Due to poor acoustic windows, M-mode and two-dimensional echocardiography was not possible in all patients (Table 3). In one patient in the DDD group who had a recent myocardial infarction before pacemaker implantation, both the left ventricular end-diastolic and end-systolic volumes increased more than 100 ml, and LVEF decreased from 0.47 to 0.21 in the period from pacemaker implant to MBF study. This patient was excluded from the analysis of the echocardiographic data, as these changes in left ventricular size and performance probably were caused by the myocardial infarction rather than by DDD pacing.

There were no differences in left ventricular diameters or volumes between the AAI and DDD groups at baseline or at the time of MBF measurements (Table 3). In the DDD group, LVEF decreased significantly from baseline to time of MBF measurements (p = 0.013, paired t test, n = 11). Furthermore, in the DDD group, LVEF measured during temporary AAI pacing at time of MBF measurements was significantly higher than during DDD mode (p < 0.001, paired t test) and not different from LVEF measured at pacemaker implantation. There were no changes in left ventricular volumes or LVEF in the AAI group.

Telemetry data and ECG. Telemetry data were obtained for 20.3 ± 8 months in the AAI group and for 20.4 ± 8 months in the DDD group. Percentage pacing in the atrium

**Table 2. MBF and Hemodynamics**

<table>
<thead>
<tr>
<th></th>
<th>AAI MBF-60</th>
<th>AAI MBF-90</th>
<th>DDD MBF-60</th>
<th>DDD MBF-90</th>
<th>DDD (DDD→AAI)-60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (mL·g⁻¹·min⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>0.57 ± 0.14</td>
<td>0.80 ± 0.10†</td>
<td>0.55 ± 0.13</td>
<td>0.80 ± 0.16†</td>
<td>0.61 ± 0.18</td>
</tr>
<tr>
<td>LCX</td>
<td>0.65 ± 0.19</td>
<td>0.92 ± 0.12†</td>
<td>0.59 ± 0.14</td>
<td>0.80 ± 0.19†</td>
<td>0.64 ± 0.18</td>
</tr>
<tr>
<td>RCA</td>
<td>0.60 ± 0.18</td>
<td>0.82 ± 0.12†</td>
<td>0.49 ± 0.17</td>
<td>0.66 ± 0.24†</td>
<td>0.59 ± 0.19*</td>
</tr>
<tr>
<td>Septum</td>
<td>0.52 ± 0.15</td>
<td>0.75 ± 0.14†</td>
<td>0.47 ± 0.16</td>
<td>0.69 ± 0.16†</td>
<td>0.59 ± 0.13*</td>
</tr>
<tr>
<td>Global mean</td>
<td>0.59 ± 0.15</td>
<td>0.82 ± 0.09†</td>
<td>0.53 ± 0.13</td>
<td>0.74 ± 0.17†</td>
<td>0.61 ± 0.15*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>126 ± 19</td>
<td>142 ± 21 †</td>
<td>127 ± 22</td>
<td>134 ± 22</td>
<td>134 ± 31</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>70 ± 16</td>
<td>78 ± 13 †</td>
<td>69 ± 11</td>
<td>81 ± 14 †</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>RPP (mm Hg·beats per min)</td>
<td>7,780 ± 1,460</td>
<td>12,752 ± 1,850†</td>
<td>7,845 ± 1,732</td>
<td>12,066 ± 2,090†</td>
<td>8,209 ± 2,253</td>
</tr>
</tbody>
</table>

Within group comparisons: ♦p < 0.01 versus MBF-60; †p < 0.0005 versus MBF-60.

AAI = single chamber atrial pacemaker; BP = blood pressure; DDD = dual chamber pacemaker; LAD = left anterior descending artery; LCX = left circumflex artery; MBF = myocardial blood flow; RCA = right coronary artery; RPP = rate pressure product = heart rate·systolic BP.

**Figure 2.** Individual global mean MBF in the single chamber atrial (AAI) and dual chamber (DDD) groups at pacing rate 60 beats/min (MBF-60) and 90 beats/min (MBF-90) and in the DDD group also during temporary pacing in the AAI mode, 60 beats/min (MBF [DDD→AAI]-60). For statistical comparisons see text and Table 2. MBF = myocardial blood flow.
was not different between groups (69 ± 34% in the AAI group and 62 ± 31% in the DDD group). On average, percentage pacing in the ventricle was 91 ± 12% in the DDD group. The QRS complex showed a left bundle branch block configuration during both MBF-60 and MBF-90 in all patients in the DDD group. At MBF-60, the QRS width was 85 ± 10 ms in the AAI group and 164 ± 29 ms in the DDD group and decreased to 93 ± 19 ms in DDD group during MBF (DDD → AAI)-60. In all patients in the DDD group, electrocardiographic signs of so called cardiac memory (24) were observed during temporary AAI pacing.

**DISCUSSION**

This study is the first to document the effects of different pacing modes on regional MBF measured quantitatively in

![Figure 3](image-url)

**Figure 3.** Individual MBF in each of the four regions in the dual chamber (DDD) group measured at pacing rate 60 beats/min (MBF-60) and 90 beats/min (MBF-90) and during temporary pacing in the AAI mode, 60 beats/min (MBF [DDD → AAI]-60). LAD, LCX and RCA indicate the three major coronary vascular territories. For statistical comparisons see text and Table 2. AAI = single chamber atrial pacing; LAD = left anterior descending artery; LCX = left circumflex artery; MBF = myocardial blood flow; RCA = right coronary artery.

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**Table 3.** Echocardiographic Findings

<table>
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<tr>
<th></th>
<th>AAI</th>
<th>DDD</th>
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<tbody>
<tr>
<td></td>
<td>At Implant</td>
<td>At MBF</td>
</tr>
<tr>
<td>M-mode echo (N)</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>49 ± 5</td>
<td>49 ± 7</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>29 ± 5</td>
<td>30 ± 9</td>
</tr>
<tr>
<td>Two-dimensional echo (N)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>LVED volume (ml)</td>
<td>85 ± 37</td>
<td>81 ± 33</td>
</tr>
<tr>
<td>LVES volume (ml)</td>
<td>35 ± 23</td>
<td>33 ± 21</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.62 ± 0.08</td>
<td>0.61 ± 0.10</td>
</tr>
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</table>

*p = 0.013 as compared with measurement at pacemaker implant.

AAI = single chamber atrial pacemaker; DDD = dual chamber pacemaker; LVED = left ventricular end-diastolic; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVES = left ventricular end-systolic; LVESD = left ventricular end-systolic diameter; MBF = myocardial blood flow.
humans. In patients with SSS, chronic DDD pacing reduces inferior, septal and global mean MBF as well as LVEF as compared with temporary AAI pacing. The LVEF reverses to baseline level during temporary AAI pacing despite 22 months of permanent ventricular pacing preceding.

**Effect of pacing mode.** This study showed differences of 4% to 20% in regional and global mean MBF between the patients treated with AAI versus those treated with DDD pacemakers. However, in the DDD group, restoration of the normal ventricular activation and contraction by altering pacing mode to AAI was associated with a significant increase in MBF in the RCA and septal regions and in the global mean MBF. These findings indicate that ventricular pacing in the DDD mode causes a decreased MBF. During pacing in the right ventricular apex, the electrical activation spreads from the pacing site through the myocardium (25), and the earliest activated parts of the left ventricle are the septum and the inferior wall (26). Therefore, in this study, ventricular pacing seemed to reduce MBF in the earliest activated parts of the left ventricle. This study, furthermore, indicates, that the reduction in regional MBF induced by ventricular pacing is reversible when the normal ventricular activation and contraction is restored despite almost two years of permanent (>90%) ventricular pacing. Chronic ventricular pacing, therefore, is apparently not associated with any irreversible reduction in regional MBF. Similarly, acute right ventricular pacing has been found to reduce septal MBF in animal studies using microsphere techniques (27,28).

In previous clinical studies, exercise perfusion scintigraphy revealed that right ventricular pacing was associated with inferior or apical myocardial perfusion defects in patients with angiographically normal coronary arteries (8,11,12). The perfusion defects, thus, were located partly in the same areas in which the MBF was found reduced during ventricular pacing in this study. However, in contrast to the reduction in MBF, the defects were found to persist after cessation of ventricular pacing (12). The mechanisms causing a reduced MBF in the early activated regions of the left ventricle are not fully understood. Experimental studies have found that the reduced MBF is associated with a reduced regional contractile work and oxygen uptake (25,29), a reduced glucose uptake (28) and a reduced systolic septal myocardial thickening (28), which indicates that the local MBF reduction represents an adaptation to a reduced oxygen need because of a reduced contractile work. An improved ventricular filling caused by AAI pacing, increasing the end-diastolic ventricular volume, improving the LVEF and increasing the physiological demand of MBF may have contributed to the increased global mean MBF during temporary AAI pacing. This phenomenon, however, cannot explain the regional differences in MBF observed when changing pacing mode from DDD to AAI.

**Left ventricular function.** In this study, the LVEF decreased during long-term DDD pacing, whereas no change was observed in the AAI group. This is in accordance with previous reports on the effects of DDD (6,7) and VVI pacing (2,30), where the decrease in LVEF is mainly caused by an increase in left ventricular end-systolic volume (2,30). In this study, the LVEF increased to the same level as measured before pacemaker implantation when the normal ventricular activation and contraction was restored, despite almost two years of permanent (>90%) ventricular pacing. This is in accordance with the experimental findings by van Oosterhout et al., who estimated left ventricular function before and after six months of dual chamber pacing (31). Previous experimental and clinical studies have indicated that chronic pacing in the apex of the right ventricle might be detrimental to the left ventricular function (8–10), an effect that has been associated with an alteration of the regional MBF (8,9). Based upon the data obtained in this study, it is still unknown whether the reduction in LVEF is caused by the alteration of regional MBF or whether these two findings are independent results of the asynchronous ventricular activation and contraction induced by ventricular pacing. The present findings, however, indicate, that a permanent two-year long local reduction in regional MBF caused by ventricular pacing does not lead to any progressive or irreversible deterioration of the left ventricular function. Whether an even longer period of ventricular pacing would cause irreversible decreases in MBF or left ventricular performance remains to be evaluated.

**Physiological and clinical interpretation of findings.** The reduction in global mean MBF observed during DDD pacing as compared with temporary AAI pacing is of the same magnitude as the reduction caused by beta-adrenergic blocking agent treatment, for example (32). The reduction in LVEF caused by DDD pacing is equal in magnitude to that observed in prior studies (5,6). The clinical importance of the reduction in regional MBF caused by right ventricular apical pacing in the DDD mode is, however, not known. The lowering of MBF and LVEF during DDD pacing may be unfavorable for some patients with preexisting congestive heart failure or coronary artery disease, which are frequent comorbidities in elderly pacemaker patients. After a mean of two years of ventricular pacing, the so called cardiac memory effect is expected to last for weeks (24), and, in fact, electrocardiographic patterns of cardiac memory were observed in this study during temporary AAI pacing in the DDD group. Therefore, it cannot be excluded that this phenomenon may have influenced the MBF measured during temporary AAI pacing.

**Effect of pacing rate.** By increasing the pacing rate up to 90 beats/min, which corresponds to the heart rate during normal daily activities in many elderly patients, an increased global mean MBF was observed in both treatment groups. This is in accordance with previous findings using rapid AAI or DDD pacing and thermodilution technique in
patients with coronary artery disease (33) or rapid AAI pacing together with $^{13}$N-labeled ammonia and dynamic PET imaging in controls and patients with hypertension (34) or dilated cardiomyopathy (35). In this study, the regional and global mean MBF at pacing rate 90 beats/min did not differ between the two groups. Increasing the paced rate to 90 beats/min in a supine, resting patient is markedly different from a heart rate increase to 90 beats/min caused by exercise. Among others, preload conditions and neurohumoral influence on the heart is different between the two situations. Augmentation of the heart rate to 90 beats/min, however, was found to be the best way to mimic activity nonpharmacologically and without disturbing the PET procedures. The quantitative effect of increasing the heart rate to 90 beats/min in this study was a similar increase in global mean MBF in the AAI group and the DDD group of 39% and 40%, respectively. Previous studies evaluating MBF during increased pacing frequency using $^{13}$N-labeled ammonia and dynamic PET imaging reported 51% to 88% increases in MBF from baseline during higher paced rates of 130 to 135 beats/min in considerably younger (mean age 47 to 54 years) individuals (34,35). The increased heart rate will tend to increase perfusion due to an increased oxygen consumption most likely by usual coronary auto regulatory mechanisms. Opposing this effect is the reduction of the diastolic filling time, which will allow shorter time for myocardial perfusion.

The effect of pacing is different from the effect of dipyridamole, which is often used to induce hyperemia. Dipyridamole increases the heart rate to approximately 90 beats/min with an only modest effect on blood pressure, as in this study, but also acts vasodilatating, and typically increases MBF 200% to 400% (15,17). Compared with similar heart rate increases during exercise, the coronary flow has been found to increase less than half during increased pacing rates (36). Acutely increasing the heart rate by means of cardiac pacing in resting patients is not caused by the need of a higher cardiac output, does not increase the myocardial contractility and is not accompanied by humoral and neural autonomic activation. This is probably the explanation of the relatively lower increase in MBF during increased heart rate as compared with pharmacological stress or exercise.

**Study limitations.** Many of the patients in this study were treated with drugs, which could potentially influence the global mean MBF, and some suffered from other diseases such as coronary artery disease, arterial hypertension or diabetes, which may also have influenced mean or regional MBF. The patients were, however, consecutive patients with SSS and normal AV conduction and can be considered representative for this elderly patient population.

Long-term ventricular pacing causes a thinning of the earliest activated parts of the ventricle (31,37), and thinning of the ventricular wall would increase the partial volume effect, thereby decreasing the recovery coefficient and the MBF measured. This phenomenon may have contributed to the regional differences found in the DDD group. However, the asymmetrical wall thickness induced by chronic pacing includes myocyte hypertrophy (31), and, therefore, cannot be acutely reversed by restoring the normal ventricular activation and contraction. In contrast, MBF increased acutely when pacing mode was changed from DDD to AAI. We have not measured ventricular wall thickness in our patients, and, therefore, we cannot rule out that differences in wall thickness between the two groups has influenced MBF measurements. Regional wall motion was not analyzed in this study. Therefore, we cannot rule out that changes in regional wall motion may have influenced comparisons of MBF during different pacing modes. The study was not powered to detect small differences in MBF between the two groups. The standard deviation in MBF was, moreover, slightly higher than expected in the power calculation, further decreasing the power of the comparisons between groups. These considerations on statistical power does not, however, affect the findings in the within-group comparisons.

**Conclusions.** In patients with SSS, chronic DDD pacing reduced inferior, septal and global mean MBF as well as LVEF as compared with temporary AAI pacing. The LVEF reversed to baseline level during temporary AAI pacing despite 22 months of permanent ventricular pacing preceding it.

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