Left Ventricular Mechanics and Myocardial Blood Flow Following Restoration of Normal Activation Sequence in Paced Patients With Long-term Right Ventricular Apical Stimulation*

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Study objectives: Asynchronous ventricular activation, as induced by ventricular pacing, is known to affect left ventricular (LV) systolic and diastolic function and myocardial blood flow. However, it is not clear whether the long-term disturbances it causes are reversible after the restoration of the normal ventricular activation sequence.

Design: In this study, we used the conductance catheter method and a Doppler guidewire to assess the changes in LV mechanics, and correspondingly in myocardial blood flow, after the restoration of the normal ventricular activation sequence in patients with long-term right ventricular apical pacing.

Patients: Sixteen patients (mean [± SD] age, 61 ± 11 years; 9 men) with right ventricular apical pacing and capture for a very long period were studied. In eight patients, we analyzed pressure-volume loops before and immediately after the restoration of the normal ventricular activation sequence, and in the remaining eight patients the myocardial blood flow and flow reserve were analyzed.

Measurements and results: End-systolic elastance (Ees) [5.50 ± 0.6 vs 4.28 ± 0.28 mm Hg/mL, respectively; p = 0.003] and its ratio to effective arterial elastance (1.63 ± 0.51 vs 2.00 ± 0.64, respectively; p = 0.009), which are indexes of systolic function and ventriculoarterial coupling, respectively, improved significantly after restoration of the normal ventricular activation sequence. Indexes of diastolic function and the predicted myocardial oxygen consumption (MV\(\dot{O}\)\(_2\)) showed no clear change. Coronary flow in the dominant coronary artery increased significantly (46.55 ± 14.12 vs 71.55 ± 27.53 mL/min, respectively; p = 0.002), while the coronary flow reserve in the same artery decreased (3.5 ± 1.0 vs 2.6 ± 0.5, respectively; p = 0.008).

Conclusions: The restoration of a normal activation sequence after long-term ventricular asynchrony enhances acutely contractile function without affecting MV\(\dot{O}\)\(_2\). These changes in LV function do not appear to have causal relationships with myocardial blood flow changes.

(CHEST 2003; 124:233–241)

Key words: left ventricular contractility; left ventricular mechanics; regional blood flow; ventricular pacing

Abbreviations: CFR = coronary flow reserve; dP/dt\(_{\max}\) = maximal rate of rise of left ventricular pressure; dP/dt\(_{\min}\) = minimal (maximal negative) rate of rise of left ventricular pressure; E\(_a\) = effective arterial elastance; Ees = end-systolic elastance; LV = left ventricle; LVEF = left ventricular ejection fraction; MV\(\dot{O}\)\(_2\) = myocardial oxygen consumption; Pes = end-systolic pressure; PRSW = preload recruitable stroke work; PWI = pressure-work index; SW = stroke work; \(\tau\) = time constant of isovolumic relaxation; Ved = end-diastolic volume; Ves = end-systolic volume

The right ventricular apex is still the most usual site for the ventricular electrode in patients who have a permanent pacemaker. The asynchronous ventricular activation and contraction that can result from this kind of pacing have a negative effect on left ventricular (LV) systolic and diastolic function,\(^{1,2}\) while also causing regional changes in myocardial perfusion\(^{3–6}\) and adren-
ergic innervation,7–9 the pathophysiologic significance of which is not yet clear.

Furthermore, long-term asynchronous ventricular activation leads to remodeling of the LV,7,10 with thinning of early-activated regions and thickening of late-activated regions,11 and also can cause histopathologic lesions in the ventricular myocardium.7,12

To date, it has not been determined whether these structural and functional disturbances that appear after long-term right ventricular apical stimulation are reversible, and if so, to what degree, following the restoration of a normal ventricular activation sequence. This is a matter of great clinical significance, since it is possible that a large number of patients with artificial pacemakers might benefit from a change in pacing mode or by adjustments that ensure as normal an activation sequence as possible.

In order to investigate the reversibility of these functional disturbances, we analyzed LV pressure-volume loops, and evaluated the LV systolic and diastolic function and ventriculoarterial coupling13–15 in patients who have received long-term pacing treatment with complete ventricular pacing capture and looked for changes immediately following the restoration of a normal activation sequence. We also studied changes in coronary flow and flow reserve, which may be related to the alteration of LV function.

**Materials and Methods**

This study included patients who were being observed in the pacing clinic and had been referred for coronary angiography because of chest pain. The inclusion criteria were as follows: (1) dual-chamber pacing with optimal AV delay for at least 1 year for sick sinus syndrome; (2) normal intraventricular conduction before pacemaker implantation and throughout the study (QRS, <110 ms); and (3) a prolonged PR interval allowing complete ventricular pacing capture at rest and during exercise (ie, to a QRS duration similar to that during VVI pacing, as established by diastolic filling time without interruption of the A wave).16,17 This was the usual procedure in our pacing clinic for the programming of DDD pacemakers in patients with a prolonged PR interval.18

The optimal AV delay was defined, using ultrasound measurements of transmural flow, as that which provided the longest diastolic filling time without interruption of the A wave.16,17 This is the usual procedure in our pacing clinic for the programming of DDD pacemakers in patients with a prolonged PR interval.18 At the time of initial pacemaker programming, the patients in this study had a particularly prolonged mean (± SD) spike-R interval during AAI pacing (ie, 270 ± 15 ms) due to a long intrinsic PR interval and the drugs they were taking (ie, β-blockers, Ca++ antagonists, and propafenone).

The exclusion criteria were as follows: (1) known history of coronary artery disease (myocardial infarction); (2) coronary arteries with stenosis of >50% of the lumen; (3) impaired LV systolic performance (ie, LV ejection fraction [LVEF], <50% [estimated during a transthoracic echocardiogram]); and (4) aortic valve stenosis or presence of a prosthetic cardiac valve.

To examine the possible alterations in LV function, we analyzed LV pressure-volume loops using a conductance catheter with a micromanometer on its tip. Additionally, we calculated the coronary flow by means of a Doppler guidewire to estimate the influence of the restoration of a normal ventricular activation sequence on the coronary circulation.

Measurements were made during DDD pacing (ie, the mode that was programmed for the long term) and 5 min after a change of pacing mode to AAI, preserving the same pacing frequency. All drugs with a possible negative inotropic and/or chronotropic effect were stopped five half-lives before the study.

All patients provided written, informed consent, and the experimental protocol was approved by the hospital ethics committee.

**Pressure-Volume Loops**

The study was performed at least 15 min after the performance of routine coronary angiography. All patients were awake and mildly sedated with diazepam, 10 mg orally.

In all cases, a Swan-Ganz catheter was used for the continuous measurement of cardiac output (thermodilution method). Subsequently, a conductance catheter with a micromanometer on its tip (7F, Millar 572–7; Millar Instruments; Houston, TX) was inserted into the LV via the right femoral artery and was utilized to estimate possible alterations in LV mechanics in the short term after the restoration of a normal LV activation sequence. We documented the proper placement of the catheter at the top of the LV radiologically and by inspecting its five segmental volume signs. The parallel conductance was calculated at least twice using the hypertonic saline solution method.

To achieve pressure-volume loops under variable preload conditions, we transiently occluded the inferior vena cava for 6 to 8 s, in the end-expiratory position, using a vascular occlusion catheter system inserted through the left femoral vein (8F, STOPFLOW catheter system; PIM; Cologne, Germany). Measurements were recorded during long-term DDD pacing and 5 min after switching the pacing mode to AAI, preserving the closest possible pacing rate.

We used a special adapter (Leycom CFL 512; Cardiodynamics BV; Zoetermeer, the Netherlands) to compute the LV total volume and to draw the LV pressure-volume loops. Data recordings were stored in the usual magnetic media and were analyzed off-line with special software (CONDUCT2000; Cardiodynamics BV).

We determined the LVEF, the LV end-systolic pressure (Pes)-end-systolic volume (Ves) relationship slope (ie, end-systolic elastance [Ees]), the LV stroke work (SW)-end-diastolic volume (Ved) relationship slope (ie, the preload recruitable SW [PRSW]), the ratio of Pes to stroke volume (SV) [ie, effective arterial elastance [Ea]], ventriculoarterial coupling (as the Ees/Ea ratio),19 and the maximal rate of rise of LV pressure (dP/dtmax)-Ved relationship from the variably loaded beats produced by transient caval occlusion during both DDD and AAI pacing modes. In addition, we estimated diastolic performance indexes as the minimum (maximal negative) rate of rise of LV pressure (dP/dtmin) and the time constant of isovolumic relaxation (τ).

Finally, we measured myocardial oxygen consumption (MVO₂) indirectly using the pressure-work index (PWI), which is well correlated with the directly measured MVO₂.20–22 To calculate the PWI, we used the following equation that has been proposed by Rooke and Feigl:22

\[
\text{PWI} = \left[ 4.08 \times 10^{-4} \times (\text{SAP} \times \text{HR}) \right] + \left[ 3.25 \times 10^{-4} \times (0.8 \times \text{SAP} + 0.2 \times \text{DAP}) \right] \times \left[ \frac{\text{HR} \times (\text{SV} / \text{BW})}{1.43} \right]
\]

where SAP is systolic arterial BP, DAP is diastolic arterial BP, HR is heart rate, and BW is body weight.
Coronary Blood Flow Measurements

A 0.014-inch, 15-MHz Doppler guidewire (FloWire; Cardio- metrics; Mountain View, CA) was used to measure coronary flow velocity in the proximal left anterior descending artery and the proximal dominant coronary artery, and the quantitative flow was calculated as the product of the vessel cross-sectional area and half of the time-averaged peak coronary flow velocity.

All measurements were made at least 5 min after the infusion of the contrast medium to the coronary vessels.

Coronary flow reserve (CFR) was defined as the ratio of coronary blood flow at maximal hyperemia (ie, after intracoronary administration of 18 μg adenosine) to that at baseline.23,24 All measurements in these arteries were recorded during DDD and AAI pacing modes.

Statistical Analysis

Continuous variables are summarized as the mean ± SD. Changes in the various parameters between DDD and AAI pacing modes were assessed with the t test for dependent samples and the Wilcoxon signed rank test. Both parametric and nonparametric tests gave significant results for the same parameters. The level of significance was set at 5%.

RESULTS

From an initial pool of 2,360 paced patients, 22 fulfilled the inclusion criteria and consented to participate in the study. In six patients, the conductance catheter signals were not satisfactory during off-line analysis, and they were all excluded. The recordings in four patients included too many extrasystoles, and the recordings were unacceptable in the remaining two patients as a result of noise due to catheter position. Finally, 16 patients (9 men; mean age, 61 ± 11 years) with a mean pacing duration of 39 ± 8 months were considered for analysis.

We examined the alterations in LV mechanics in eight patients (five men; mean age, 59 ± 10 years) and changes in coronary flow in the remaining eight patients (four men; mean age, 63 ± 12 years) using a conductance catheter with a micromanometer on the tip and a Doppler guidewire, respectively. Patients in the LV mechanics group (group 1) and the coronary flow measurements group (group 2) had similar clinical characteristics (Table 1).

LV Systolic Performance

After restoration of a normal ventricular activation sequence, the Ees increased significantly (4.287 ± 0.28 mm Hg/mL vs 5.503 ± 0.59 mm Hg/mL, respectively; p = 0.003), suggesting that intrinsic myocardial contractility was enhanced (Fig 1). Similarly, LVEF (46 ± 4.7% vs 49 ± 4.7%, respectively; p = 0.002), PRSW (91.78 ± 6.14 mm Hg vs 100.99 ± 12.32 mm Hg, respectively; p = 0.033), and the ventriculaoarterial coupling index Ees/Ea (1.63 ± 0.51 vs 2.00 ± 0.64, respectively; p = 0.009) also increased significantly. Although dP/ dtmax did not change, its correlation to end diastolic volume (dP/dtmax–Ve), which is a preload-insensitive and afterload-insensitive contractile index,25 improved during AAI pacing (73.48 ± 3.2 mm Hg/s/mL vs 77.48 ± 4.7 mm Hg/s/mL, respectively; p = 0.002).

There were no statistically significant differences in cardiac and stroke index, SW, LV Pes or Ves, and MVO2 (Table 2).

LV Diastolic Performance

Of the diastolic performance indexes evaluated in our study, only dP/dtmin was altered significantly following the restoration of a normal ventricular activation sequence (−1,509 ± 160 mm Hg/s vs −1,550 ± 177 mm Hg/s, respectively; p = 0.038). However, more specific indexes of diastolic function, such as τ, showed no clear change (44.0 ± 5.6 ms vs 45.4 ± 4.7 ms, respectively; p = 0.105) [Table 2].

Coronary Flow and CFR Measurements

No patient had any mild or severe arterial obstruction in any region of a vessel where measurements were obtained.

Left Anterior Descending Artery

The restoration of the normal activation sequence caused a slight but nonsignificant increase in baseline coronary flow (increase, 145.0 ± 30.1 to 157.6 ± 32.7 mL/min; p = 0.083), while the coronary flow during maximal hyperemia did not change significantly (346.7 ± 77.9 mL/min vs 341.0 ± 71.0 mL/min, respectively; p = 0.421). As a result, CFR

Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr† (mean ± SD)</td>
<td>59 ± 10</td>
<td>63 ± 12</td>
<td>0.416</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>4</td>
<td>5</td>
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</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0</td>
<td>1</td>
<td>0.211</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>3</td>
<td>3</td>
<td>0.814</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>4</td>
<td>3</td>
<td>0.353</td>
</tr>
<tr>
<td>Therapy</td>
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</tr>
<tr>
<td>ACE inhibitors</td>
<td>4</td>
<td>5</td>
<td>0.419</td>
</tr>
<tr>
<td>β-blockers</td>
<td>4</td>
<td>5</td>
<td>0.530</td>
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<tr>
<td>Calcium channel blockers</td>
<td>2</td>
<td>1</td>
<td>0.174</td>
</tr>
<tr>
<td>Propafenone</td>
<td>4</td>
<td>3</td>
<td>0.299</td>
</tr>
</tbody>
</table>

*NS = not significant; ACE = angiotensin-converting enzyme.
†Values given as No., unless otherwise indicated.

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also did not change significantly (2.5 ± 0.7 vs 2.3 ± 0.6, respectively; \( p = 0.326 \)) [Table 3].

**Dominant Coronary Artery**

In five patients, the dominant artery was the right coronary artery, while in the other three patients the dominant artery was the circumflex artery. The restoration of a normal activation sequence caused a significant increase in baseline coronary flow (increase, 46.6 ± 14.1 to 71.7 ± 27.5 mL/min; \( p = 0.002 \)), while the coronary flow during maximal hyperemia did not change (178.2 ± 57.8 mL/min vs
177.1 ± 55.7 mL/min, respectively; p = 0.511), resulting in a significant reduction in CFR (reduction, 3.5 ± 1.0 to 2.6 ± 0.5; p = 0.019) [Table 3 and Fig 2].

**DISCUSSION**

The new findings of this study are as follows: (1) the restoration of a normal ventricular activation sequence after long-term right apical stimulation improves LV contractility and ventriculoarterial coupling in the short term but has no significant effect on diastolic function and MVO₂; and (2) the change from long-term asynchronous ventricular activation to synchronous ventricular activation leads to a significant increase in the flow in the dominant coronary artery, while reducing the flow reserve in the same artery.

**LV Function and Ventriculoarterial Coupling**

Previous studies have shown that right ventricular apical stimulation has a negative inotropic effect and also leads to disturbances of LV diastolic function. A study by Tantengco et al examined 24 young patients with normal segmental anatomy who received pacing from the right ventricular apex for a mean period of 9.5 years. They underwent noninvasive assessment of global LV function with the fractional area of change derived from automated border detection echocardiography, coupled with

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**Table 2—LV Mechanics During Long-term DDD Pacing and Immediately After Switching to AAI Pacing Mode**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>DDD</th>
<th>AAI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65.42 ± 10.42</td>
<td>64.97 ± 7.03</td>
<td>0.103</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>204 ± 16</td>
<td>91 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stimulus-to-R interval, ms</td>
<td>137 ± 14</td>
<td>215 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LV systolic performance indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ves, mL</td>
<td>61 ± 11.68</td>
<td>58 ± 11.23</td>
<td>0.129</td>
</tr>
<tr>
<td>Pes, mm Hg</td>
<td>96.6 ± 17.5</td>
<td>95.2 ± 17.1</td>
<td>0.205</td>
</tr>
<tr>
<td>Stroke index, mL/m²</td>
<td>46 ± 10.5</td>
<td>47 ± 11.4</td>
<td>0.734</td>
</tr>
<tr>
<td>Cardiac index, L/min/m²</td>
<td>4.42 ± 0.43</td>
<td>4.29 ± 0.63</td>
<td>0.574</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>46 ± 4.7</td>
<td>49 ± 4.7</td>
<td>0.002</td>
</tr>
<tr>
<td>SW, mm Hg/mL</td>
<td>5.694 ± 768</td>
<td>5.494 ± 426</td>
<td>0.517</td>
</tr>
<tr>
<td>PRSW, mm Hg</td>
<td>91.8 ± 6.1</td>
<td>100.9 ± 12.3</td>
<td>0.033</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
<td>1449 ± 129</td>
<td>1439 ± 122</td>
<td>0.759</td>
</tr>
<tr>
<td>dP/dtmax-Ved slope, mm Hg/s/mL</td>
<td>73.48 ± 3.2</td>
<td>77.48 ± 4.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Es, mm Hg/mL</td>
<td>4.287 ± 0.28</td>
<td>5.503 ± 0.60</td>
<td>0.003</td>
</tr>
<tr>
<td>LV mechanical efficiency indexes</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ea, mm Hg/mL</td>
<td>2.88 ± 1.03</td>
<td>3.05 ± 1.19</td>
<td>0.273</td>
</tr>
<tr>
<td>Ventriculoarterial coupling index</td>
<td>1.63 ± 0.51</td>
<td>2.00 ± 0.64</td>
<td>0.009</td>
</tr>
<tr>
<td>MVO₂, mL O₂/min/100 g</td>
<td>7.035 ± 0.74</td>
<td>7.058 ± 0.73</td>
<td>0.993</td>
</tr>
<tr>
<td>LV diastolic performance indexes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ved, mm Hg</td>
<td>136 ± 17</td>
<td>133 ± 16</td>
<td>0.427</td>
</tr>
<tr>
<td>End-diastolic pressure, mm Hg</td>
<td>10.55 ± 0.8</td>
<td>10.59 ± 1.2</td>
<td>0.935</td>
</tr>
<tr>
<td>dP/dtmin, mm Hg/s</td>
<td>-1,509 ± 160</td>
<td>-1,550 ± 177</td>
<td>0.038</td>
</tr>
<tr>
<td>τ, ms</td>
<td>44.0 ± 5.6</td>
<td>45.4 ± 4.7</td>
<td>0.105</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated.

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**Table 3—Coronary Blood Flow Measurements at Baseline and at Maximal Hyperemia During DDD and AAI Pacing Modes**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left Anterior Descending Artery</th>
<th>Dominant Coronary Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DDD</td>
<td>AAI</td>
</tr>
<tr>
<td>Baseline coronary blood flow, mL/min</td>
<td>145.0 ± 30.1</td>
<td>157.6 ± 32.7</td>
</tr>
<tr>
<td>Hyperemic coronary blood flow, mL/min</td>
<td>346.7 ± 77.9</td>
<td>341.0 ± 71.0</td>
</tr>
<tr>
<td>CFR</td>
<td>2.5 ± 0.7</td>
<td>2.3 ± 0.6</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD, unless otherwise indicated.
Doppler indexes of myocardial performance. The patients demonstrated impaired regional and Doppler flow-derived indexes of LV systolic and diastolic function compared with control subjects. In short-term studies, it has been shown that a change of pacing mode from DDD to AAI results in an increase of coronary flow during baseline and hyperemia.

**Figure 2.** Doppler recording of coronary blood flow velocity (in centimeters per second) in the circumflex artery during DDD pacing (left panels) and AAI pacing (right panels). During AAI pacing, the coronary flow is increased compared to DDD pacing at baseline (top left, A, and top right, B), while it remains constant during hyperemia (bottom left, C, and bottom right, D). Volumetric flow corresponds to the product $0.5 \times$ average peak velocity $\times$ cross-sectional area. The cross-sectional area remains constant in both cases.
improvement of LV contractility and mechanical energy efficiency.26–29 In patients receiving long-term pacing, however, apart from the functional changes that asynchronous ventricular activation entails, there are likely to be histologic disturbances and LV remodeling.7,10–12

In this study, we found that in such patients Ees, which is perhaps the most objective contractility index that is independent of LV loading, increased significantly a few minutes after a normal ventricular activation sequence was restored. This means that long-term asynchronous ventricular activation leads to LV contractile dysfunction that is, at least in part, reversible immediately after the restoration of a normal ventricular activation sequence. In a study by Nielsen et al.,6 it was found that a change in pacing mode from DDD to AAI in patients receiving long-term pacing (ie, mean duration of pacing, 22 ± 8 months) caused an immediate and significant increase in LVEF. However, the latter is only a rough index of systolic function, being load-dependent, and so no sure conclusions can be drawn regarding changes in myocardial contractility following an alteration of pacing mode. In contrast to the systolic indexes, the diastolic indexes we evaluated, apart from dP/dtmin, showed no significant changes.

In fact, we cannot explain the increase in the magnitude of dP/dtmin while other, more objective indexes of LV relaxation (such as τ) did not change significantly. Accordingly, it may be a potential statistical error, due to the small number of patients studied. On the other hand, it has been found30 that, following long-term asynchronous ventricular activation, the disturbances of diastolic function begin to regress 24 h after the restoration of a normal ventricular activation sequence. In the present study, we also found that the Ees/Ea ratio, which expresses ventriculoarterial coupling, increased significantly after the restoration of a normal ventricular activation sequence and that the predicted MVO₂ remained unchanged.

Although MVO₂ had no clear change, in contrast to the situation after the use of most positive inotropic agents,31,32 the improvement of contractility should be attributed to the more “economic” function of the heart and to the improved ventriculoarterial coupling after the restoration of a normal ventricular activation sequence. Our results are relevant to those of Nelson et al.,33 who found that cardiac resynchronization in patients with dilated cardiomyopathy and left bundle branch block improved LV contractile function with a modest decline in oxygen utilization.

We also speculate that the restoration of a normal LV activation sequence in our patients does not affect intrinsic myocyte function but rather provides its net effect by the enhancement of the effective-

Coronary Flow and CFR

In this study, we found that, in patients receiving long-term DDD pacing, the resting flow in the dominant coronary artery increases significantly immediately after the restoration of a normal ventricular activation sequence. This finding is in agreement with that of Nielsen et al.,6 who used 13-N-labeled ammonia positron emission tomography scanning for myocardial blood flow quantification. We also found that the CFR in the same artery is reduced significantly during the change of pacing mode to AAI.

Previous studies5,34–37 have shown that, in patients receiving long-term pacing through the right ventricular apex, both the baseline coronary flow and the coronary flow during maximal hyperemia are impaired in comparison with healthy control subjects. These findings have been attributed to changes in the regulation of coronary flow due to functional and/or structural abnormalities induced by permanent ventricular pacing.

According to our findings, the restoration of a normal activation sequence improves baseline coronary flow significantly in the dominant coronary artery but does not affect coronary flow during maximal hyperemia. The above findings are probably due to the fact that the restoration of a normal ventricular activation sequence blunts functional abnormalities in the short term but has a small effect or no effect on the structural abnormalities induced by permanent right ventricular apical pacing. Besides, the fact that the observed functional abnormalities during ventricular pacing, like reduced regional myocardial work, reduced oxygen uptake, and free fatty metabolism, are found in regions supplied by the dominant artery further reinforces our results.34

Previous studies2,4,27 have speculated that the impairment of LV systolic function is due to the reduction in coronary flow that is seen in patients receiving long-term pacing. However, the fact that systolic function improves following the restoration of a normal ventricular activation sequence, whereas CFR worsens, suggests that these changes are probably independent of the asynchronous ventricular activation induced by right ventricular apical pacing.

Study Limitations

Although the LV contractility in our patients improved significantly, we are unable to know whether it reached its prepacing levels, since prepacing mea-
measurements of Ees were not available to us. Furthermore, the evaluation of systolic and diastolic functional indexes was made only a few minutes after the restoration of a normal ventricular activation sequence. It would be interesting to investigate whether the improvement in systolic function would continue over the following hours or days, and whether an improvement would be seen in diastolic function, in which we observed no clear short-term change. Coronary flow and CFR also might exhibit different behavior if they were evaluated some time after the restoration of a normal ventricular activation sequence.

Clinical Implications

For a number of reasons, which vary from country to country and from one pacing center to another, right ventricular apical pacing under VVI or DDD pacing modes is common. The findings of this study demonstrate that patients who receive pacing in this way can expect to benefit from the restoration of a more normal ventricular activation sequence even after long-term ventricular asynchrony.

Conclusions

The restoration of a normal ventricular activation sequence after long-term ventricular asynchrony enhances the short-term contractile function without affecting MVO₂. These changes do not seem to relate to myocardial blood flow changes. Although more studies are needed to examine whether the improvement in LV contractility translates into a clinical benefit, it seems reasonable to restore a normal activation sequence where possible, even following long-term ventricular asynchrony.

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