Mismatch between uniform increase in cardiac glucose uptake and regional contractile dysfunction in pacing-induced heart failure

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THE FAILING HEART DISPLAYS profound alterations in energy substrate metabolism, characterized by reduced fatty acid oxidation and increased glucose utilization (45). Experimental and clinical data indicate that a higher reliance on glucose as the source of energy might play an important pathophysiological role. We tested whether, similar to functional derangement, changes in glucose uptake develop following a regional pattern. Heart failure was induced in 13 chronically instrumented minipigs by pacing the left ventricular (LV) free wall at 180 beats/min for 3 wk. Regional changes in contractile function and stress were assessed by magnetic resonance imaging, whereas regional flow and glucose uptake were measured by positron emission tomography utilizing, respectively, the radiotracers [13N]ammonia and 18F-deoxyglucose. In heart failure, LV end-diastolic pressure was 20 ± 4 mmHg, and ejection fraction was 35 ± 4% (all P < 0.05 vs. control). Sustained pacing-induced dysynchronous LV activation caused a more pronounced decrease in LV systolic thickening (7.45 ± 3.42 vs. 30.62 ± 8.73%, P < 0.05) and circumferential shortening (−4.62 ± 1.0 vs. −7.33 ± 1.2%, P < 0.05) in the anterior/anterolateral region (pacing site) compared with the inferoseptal region (opposite site). Conversely, flow was reduced significantly by ~32% compared with control and was lower in the opposite site region. Despite these nonhomogeneous alterations, regional end-systolic wall stress was uniformly increased by 60% in the failing LV. Similar to wall stress, glucose uptake markedly increased vs. control (0.24 ± 0.004 vs. 0.07 ± 0.01 μmol·min⁻¹·g⁻¹, P < 0.05), with no significant regional differences. In conclusion, high-frequency pacing of the LV free wall causes a dysynchronous pattern of contraction that leads to progressive cardiac failure with a marked mismatch between increased glucose uptake and regional contractile dysfunction.

heart failure; pacing; mismatch; dyssynchrony; glucose uptake

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MATERIALS AND METHODS

Surgical Instrumentation

Thirteen male, sexually mature minipigs (35–40 kg) were sedated with a cocktail of tiletamine hydrochloride and zolazepam hydrochlo-
ride \((8\ \text{mg/kg}\ \text{bm})\) and premedicated with atropine sulfate \((0.1\ \text{mg/kg}\ \text{bm})\). General anesthesia was subsequently induced with propofol \((2–4\ \text{mg/kg}\ \text{iv})\) and maintained with \(1–2\%\ \text{isoflurane in 60}\%\ \text{air and 40}\%\ \text{oxygen}\). Ventilation was adjusted based on arterial blood gas values. The pigs were chronically instrumented following a variant of a previously described protocol \((37)\). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

**Experimental Protocol**

HF was induced by pacing the LV at 180 beats/min for 3 wk. The stimulus amplitude was 2.5 volts, and the pulse duration 0.5 ms. We found that this pacing rate, lower compared with those used in other studies, was best tolerated by the majority of pigs and was equally efficacious in inducing severe LV dysfunction. Pigs were considered in severe HF when LV end-diastolic pressure was \(\geq 20\ \text{mmHg}\). We chose not to wait for decompensated HF, since at that terminal stage the animals would have not tolerated long MRI and PET procedures. Hemodynamic measurements and diagnostic imaging were performed after overnight fasting in minipigs sedated with continuous infusion of midazolam \((0.1\ \text{mg/kg}^{-1}\cdot\text{h iv})\) at spontaneous breathing. It was previously shown that similar doses of midazolam exert an irrelevant effect on cardiac contractile function \((42)\). Hemodynamic measurements, MRI, and PET were performed at baseline and in HF. The experiments were performed at spontaneous heart rate, with the pacemaker turned off, and during pacing stress, with the pacemaker turned on. The minipigs were finally killed by injecting saturated KCl solution intravenously after deep sedation with 1 mg/kg of midazolam.

Animal instrumentation and experimental protocol were approved by the Animal Care Committee of the Italian Ministry of Health and was in accordance with the Italian law (DL-116, Jan. 27, 1992), which is in compliance with the National Institutes of Health publication Guide for the Care and Use of Laboratory Animals.

**Hemodynamic Recordings**

Hemodynamic data were obtained from sedated animals at spontaneous heart rate after the pacemaker had been inactivated for at least 30 min \((31, 37)\). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

**Cardiac MRI and PET**

Regional LV myocardial perfusion and glucose uptake were measured by PET, whereas regional contractility was quantified by conventional and tagging MRI. For both types of imaging, we used three cross-sectional planes, i.e., basal, middle, apical, and six circumferential regions, i.e., anterior, anterior-lateral, inferolateral, inferior, inferoseptal, anterior-septal. For our analysis, we selected LV regions close to the site of pacing, i.e., the anterior and anterior-lateral, named pacing site, and remote from the pacing site, i.e., the inferior and septal-inferior, named opposite site.

**MRI Measurements**

Global LV function, Cine-MRI Images were acquired with a 1.5-Tesla MRI scanner (Signa Excite HD; GE Medical Systems, Waukesha, WI) with maximal gradient intensity 50 mT/m and slew rate 150 T·m⁻¹·s⁻¹, using a non-breath-hold electrocardiogram (ECG)-gated, steady-state free-precession pulse sequence (FIESTA ASSET; see Ref. 13). The pigs were lightly sedated \((0.1\ \text{mg·kg}^{-1}·\text{h}^{-1}\ \text{iv midazolam})\) and placed in the right lateral position with the heart at the isocenter of the MRI unit, and ECG and aortic pressure were monitored continuously. We couldn’t measure LV pressure because of interference of the magnetic field with the intraventricular transducer. Global LV parameters (end-diastolic volume, end-systolic volume, and ejection fraction) and systolic wall thickness in each LV region \((35)\) were analyzed with a commercially available research software package (Mass Analysis, Leyden, The Netherlands). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

Regional wall displacement and mechanical dyssynchrony. We determined LV regional displacement toward or away from the anatomic centroid of the heart during cardiac cycle. For this quantitative assessment of wall motion, we used cyclic changes in LV radius \((R)\) measured according to a method previously described by Balzer et al. \((6)\) and in part modified by us. First, we determined the LV radii at the pacing and opposite site in the short-axis images (Fig. 1, A and B): in each short-axis view, we positioned the LV center, named centroid \((c)\), and automatically traced 72 radii, 5° apart, from the centroid to the endocardial contour. A 0° angle of reference was manually fixed at the level of the junction between the LV inferior septum and the inferior wall. \(R\) was then corrected by the three-dimensional angle of curvature of the LV wall. As shown in Fig. 1, A and B, the point where a radius intersected the endocardial contour was named vertex \((V)\). Each vertex was defined by the following four coordinates: the \(x\) and \(y\) coordinate in the short-axis plane (Fig. 1A), the angle of the respective \(R\) in the short-axis plane (Fig. 1A), and the \(z\) coordinate along the long LV axis (Fig. 1B). These coordinates were used to reconstruct a three-dimensional mesh of the LV during the cardiac phase. We then determined the instantaneous longitudinal angle of curvature \((\alpha)\) (Fig. 1B) of each LV slice during cardiac cycle. The \(\alpha\) was measured using the coordinates of two contiguous vertices \((V1, V2)\) from two slices characterized by an identical angle of the respective radii and therefore placed along the same longitudinal plane (Fig. 1B). This angle was necessary to identify the anatomic centroid \((c')\), i.e., the point of intersection between the LV long axis and perpendicular to the wall tangent \(V1-V2\). We then calculated the angle \(\gamma\) as \(90° - \alpha\). Having these elements in our hands, we could calculate the corrected radius \(R'\) as

\[
R' = R \cos \gamma
\]

\(R'\) corresponded to the distance between \(VI\) and the respective \(c'\) (Fig. 1B) and was used to determine LV displacement during the cardiac cycle. LV slices were first grouped as basal (between atrioventricular plane and papillary muscles), middle (at papillary level), and apical (below papillary insertion). Next, we calculated the average anatomic centroid for each group of slices: basal, middle, and apical (Fig. 1, C and D). All of the \(R'\) in each group were used to calculate a mean vector, basal, middle, and apical, departing from the respective anatomic centroid and ending at the endocardial surface (Fig. 1, C and D). Instantaneous variations of direction and magnitude of this vector provided an index of LV regional displacement during the cardiac cycle. Mechanical dyssynchrony was quantified by comparing the time-to-peak systolic radial displacement \(\left(T_{\text{max}}\right)\); see Ref. 39) in the pacing site with the opposite site.

**Regional wall stress.** \(R'\), measured as above, was also used to calculate end-systolic wall stress in the basal and middle regions of pacing and opposite sites using in house custom made software. We employed the method established by Balzer et al. \((6)\), in part modified by us. Specifically, we used the following equation:

\[
\text{EWS} = 0.133 \times \text{SAP} \times \frac{R'}{2T} \times \left(1 - \frac{T}{2R'}\right)
\]

where SAP is the end-systolic blood pressure in aorta identified at the dicrotic notch, 0.133 is the factor to convert in \(10^3\ \text{N/m}^2\), end-systolic
is the corrected radius defined above and \( T \) is the corrected end-systolic thickness (Fig. 1A).

\( T \) was calculated based on angle between \( R \) and \( R' \):

\[
T' = \frac{T}{\cos \gamma}
\]  

(3)

This correction was necessary, since the wall thickness is overestimated if simply measured along the short axis.

To identify the end-systolic \( R' \) and \( T' \) in different cardiac regions, we used a common reference, i.e., the minimum LV volume.

Regional LV contractility. Regional contractility was assessed by employing two indexes, i.e., systolic wall thickening and circumferential strain, in three short-axis segments (basal, middle, and apical) for correlations with matched PET slices. Slices located between the atrioventricular plane and papillary muscles were defined as basal, slices at the papillary level were defined as middle, and slices below the papillary insertion were defined as apical.

End-systolic wall thickening was calculated as:

\[
\text{EST} = \frac{\text{EST} - \text{EDT}}{\text{EDT}} \times 100
\]  

(4)

where EST was end-systolic thickness and EDT was end-diastolic thickness.
Two-dimensional maximal circumferential strain was measured using tagging MRI, following an acquisition protocol previously used by us (38). In each of the above-mentioned regions, we assessed contractile strain from three different layers of the myocardial wall (endocardial, midmyocardial, and epicardial), although we presented data relative only to the midmyocardial layer. End-systolic circumferential strain was then calculated as previously described (38). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.) Both end-systolic thickness and strain for different LV regions were identified using a common reference, i.e., the minimum LV volume.

Myocardial perfusion. Myocardial perfusion was assessed with the first-pass technique (3) with the pacemaker turned off. This assessment was not repeated with the pacemaker on to shorten the MRI protocol. A bolus of gadolinium diethylenetriamine pentaacetic acid (0.05 mmol/kg at 4 ml/s of infusion velocity iv Gd-DTPA; Magnevist, Schering, Berlin, Germany) was injected in a peripheral vein. Analysis of regional perfusion was performed using a dedicated software named Hypo-perfusion and previously validated by us (33). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

Myocardial fibrosis. To assess the presence of tissue fibrosis, gadolinium-delayed contrast-enhanced images were acquired in two-dimensional segmented inversion recovery-prepared gradient echo-sequence 10 min after administration of contrast agent Gd-DTPA (0.2 mmol/kg iv) in short-axis views (25, 49). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

PET Measurements

All animals were scanned on a two-ring positron tomograph ECAT HR Plus (Siemens; CTI, Knoxville, TN) with a spatial resolution of 5 mm full width at half-maximum (32 rings of bismute germanium detectors; 63 simultaneous cross-sectional planes for a field of view of 15 cm) in the right lateral decubitus under light sedation with midazolam (0.1 mg·kg⁻¹·h⁻¹ iv) after overnight fasting. During image acquisition, heart rate, aortic pressure, coronary blood flow, and ECG were recorded continuously. Correct positioning was maintained throughout the study with the use of the light beam and marks on the pig torso. Myocardial perfusion was assessed by [¹⁸F]deoxyglucose and glucose uptake were calculated with graphical analysis according to the method of Patlak et al. (32) using the software previously mentioned (Munich Heart; NM Software). (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

Plasma glucose and insulin measurements. Arterial glucose and insulin concentration were measured by employing standard methods (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

Data Analysis

To simplify analysis and presentation, data relative to LV basal, middle, and apical segments were averaged to obtain only one value for the pacing site and one for the opposite site. Statistical comparisons were then made between pacing and the opposite site. For the calculation of T max we used only the middle segment for the pacing and for the opposite site. We chose that particular segment because it gave the best MRI signal.

Data are presented as means ± SE. Statistical analysis was performed by employing commercially available software (SPSS for Windows, version 11.1; SPSS, Chicago, IL). Hemodynamic, myocardial perfusion, and metabolic changes at different time points in the same group and differences between groups were compared by one- and two-way ANOVA followed by the Bonferroni post hoc test. For all statistical analyses, significance was accepted at P < 0.05.

RESULTS

Hemodynamics and LV Global Function

LV end-diastolic pressure reached 20 mmHg after 21 ± 4 days of pacing. We considered this as a stage of severe, although not terminal, HF. As shown in Table 1, hemodynamics displayed the typical alterations previously found by us and by others (23, 30, 37) in this model of HF, with increased heart rate, marked decrease in LV and aortic pressure, and no significant changes in blood flow measured in an epicardial coronary artery. Coronary blood flow did not increase significantly when the pacemaker was turned on at control (24.9 ± 3.07 vs. 27.5 ± 2.63 ml/min) and in HF (20.23 ± 4.43 vs. 20.24 ± 4.8 ml/min). Global cardiac function was depressed, as indicated by a fall in dP/dmax, ejection fraction, and fractional shortening of the short-axis LV diameter. Interestingly, although LV end-diastolic diameter was increased by ~20%, MRI measurements indicated that end-diastolic volume was not significantly different from control.

Regional LV Displacement and T max

Figure 2A shows an example of regional radial displacement and LV volume changes during the systolic phase at control and in HF. In the normal heart at spontaneous heart rate, pacing and opposite site contracted in a synchronous fashion, and their displacement was paralleled by changes in volume. When the pacemaker was turned on, not only did the pacing site have a more limited displacement compared with the opposite site, but it reached T max earlier and before the completion of LV systolic ejection. After 21 days of incessant pacing...

Table 1. Hemodynamics and LV diameters, volumes, and global contractile function

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>21 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>13</td>
<td>88.16 ± 4.6</td>
<td>115.66 ± 7.6*</td>
</tr>
<tr>
<td>CBF, ml/min</td>
<td>9</td>
<td>24.9 ± 0.7</td>
<td>20.23 ± 4.43</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>13</td>
<td>105.3 ± 7.2</td>
<td>80.3 ± 7.2*</td>
</tr>
<tr>
<td>LVDP, mmHg</td>
<td>11</td>
<td>6.4 ± 1.06</td>
<td>20.37 ± 3.05*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>11</td>
<td>123.3 ± 12.43</td>
<td>96.2 ± 7.9*</td>
</tr>
<tr>
<td>LV dP/dmax, mmHg/s</td>
<td>11</td>
<td>22.33 ± 246.60</td>
<td>1.436 ± 151.21*</td>
</tr>
<tr>
<td>LVESV, cm</td>
<td>7</td>
<td>3.6 ± 0.25</td>
<td>4.3 ± 0.30*</td>
</tr>
<tr>
<td>LVESD, cm</td>
<td>7</td>
<td>1.54 ± 0.34</td>
<td>3.5 ± 1.02*</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>7</td>
<td>69.16 ± 4.78</td>
<td>82.6 ± 7.0</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>7</td>
<td>18.5 ± 1.91</td>
<td>47.83 ± 5.0*</td>
</tr>
<tr>
<td>EF, %</td>
<td>7</td>
<td>75.6 ± 1.84</td>
<td>34.8 ± 3.5*</td>
</tr>
<tr>
<td>FS, %</td>
<td>7</td>
<td>44.1 ± 1.9</td>
<td>17.5 ± 2.55*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of experiments. HR, heart rate; MAP, mean arterial pressure; CBF, mean coronary blood flow; LVDP, left ventricular (LV) end-diastolic pressure; LVSP, LV systolic pressure; LVEDV, LV end-diastolic diameter; LVEDV, LV end-systolic diameter; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume; EF, ejection fraction; FS, fractional shortening of the LV short-axis diameter. *P < 0.05 vs. control.
pacing, this time delay between the two sites was still present when the pacemaker was on and was maintained even at spontaneous heart rate. $T_{\text{max}}$ values for the two sites in the various conditions are summarized in Fig. 2B while Fig. 2C shows differences in $R'$ at the end-systolic point, corresponding to the minimum LV volume. There was a significant difference between pacing and the opposite site during pacing. At 21 days, not only was the difference significant when the pacemaker was turned on, but also at spontaneous heart rate. A tridimensional reconstruction of LV displacement in normal and failing hearts is provided in the data supplements. (Supplemental material for this paper may be found on the American Journal of Physiology: Heart and Circulatory Physiology web site.)

Regional LV Wall Thickening and End-Systolic Circumferential Strain

Systolic LV wall thickening, an index of regional contractile function, was reduced significantly by acute pacing at control (Fig. 3A). At 21 days of pacing, it was further reduced by $\sim 88$ and $49\%$ in the pacing and opposite site, respectively, with a significant difference between the two sites that was present also at spontaneous heart rate.

$Ecc_{\max}$, a second index of regional contractility, did not change significantly during acute pacing at control (Fig. 3B). At 21 days of pacing, it was reduced by $\sim 69\%$ in both LV sites compared with control when the pacemaker was on. At spontaneous heart rate, however, such a decrease in circumferential

Fig. 2. Regional LV radial displacement and time-to-peak systolic radial displacement ($T_{\text{max}}$). A: averaged segmental radial displacement and volume curves in two regions of interest. Arrows, peak systolic radial displacement. B: mean values for $T_{\text{max}}$ in pacing and opposite site; $n = 7$ experiments. C: mean values for end-systolic corrected radius ($R'$) in pacing and the opposite site; $n = 7$. $P < 0.05$ vs. corresponding experimental condition at control (*), vs. pacing off at the same time point (†), and pacing site vs. opposite site (#).
shortening was found only in the pacing site, with a significant difference between the two sites, indicating the presence of a regional, rather than global, contractile alteration.

LV End-Systolic Wall Stress

LV end-systolic wall stress was not affected by acute pacing in the healthy heart (Fig. 4). After 21 days of pacing, wall stress was increased significantly in both LV sites by ~60%, either with the pacemaker on and off. Therefore, in contrast with contractile function, changes in end-systolic wall stress did not present regional differences.

MRI-Measured Myocardial Perfusion and Viability

Figure 5A shows a representative case of first-pass segmental time-signal intensity curves through different LV wall regions at spontaneous heart rate in normal and failing heart. Numerical values summarized in Fig. 5B indicate that, at control, there was no significant difference between relative upslopes in the pacing compared with the opposite site. In HF, however, the upslope was higher in the opposite site, indicating a significant relative hypoperfusion of the pacing site.

The regional analysis of gadolinium-delayed contrast enhancement images did not show any significant difference between the two sites and between control and HF (data not shown). Therefore, we could exclude the presence of infarcted areas and/or gross myocardial fibrosis after 21 days of pacing.

PET-Measured Myocardial Blood Flow

As shown in the representative case in Fig. 6A, myocardial blood flow increased in response to acute pacing stress in the normal heart. Data in Fig. 6B indicate that this increase was not homogeneous and more pronounced in the pacing site (37.5%) than in the opposite site (28.5%). However, in HF, flow was reduced by ~32% at spontaneous heart rate compared with control, remained unchanged during pacing, and was significantly lower in the opposite compared with the pacing site. Therefore, not only did HF cause a marked decrease in PET-measured myocardial blood flow with regional differences, but it also impaired the flow response to pacing stress.

Myocardial Glucose Uptake and Plasma Insulin

The representative case in Fig. 7A provides visual evidence of the extremely low myocardial glucose uptake in a normal heart at spontaneous rate, while PET signal intensity becomes very strong in the failing heart. As shown in Fig. 7B, at control, glucose uptake increased by ~125% in response to acute pacing stress, with no significant differences between pacing and the opposite site. After 21 days of pacing, glucose uptake was markedly (150%) and globally increased at spontaneous heart rate compared with control. Surprisingly, in HF, pacing stress did not further enhance but rather decreased glucose uptake in both sites compared with spontaneous heart rate. Plasma glucose levels were not significantly different in pigs with HF compared with control (4.9 ± 0.3 vs. 4.6 ± 0.2 mmol/l). On the other hand, plasma insulin concentration was increased from 25.2 ± 2.33 pmol/l at control to 47.4 ± 1.94 in HF (n = 5, P < 0.05).

DISCUSSION

The present study shows that sustained mechanical dyssynchrony induced by continuous LV rapid pacing causes a homogeneous increase in myocardial glucose uptake despite pronounced regional differences in LV contractility. The territory-independent enhancement of glucose uptake was consistent with a uniform increase in LV systolic wall stress, which...
is a major determinant of cardiac metabolic demand. Moreover, we found a clear mismatch between augmented wall stress or glucose uptake and a marked decrease in myocardial perfusion assessed by PET.

Chronic dyssynchronous contraction is a known deleterious factor with a negative prognostic value in the progression of HF (5, 17, 40). Its effects on global and regional cardiac mechanics have been extensively described by other authors in humans and in animal models (4, 8–9, 18, 34–36, 46).

The specific focus of the present study was on the potential match or mismatch, in the failing heart, between regional alterations in LV contraction, stress and flow, and altered cardiac glucose consumption. To our knowledge, no prior studies have determined regional changes in function and glucose uptake in pacing-induced HF by employing both of MRI and PET.

In this model of rapidly evolving dilated cardiomyopathy, we could compare the acute effects of pacing on regional function and glucose uptake in healthy hearts with those occurring at a stage of severe systolic dysfunction. The pattern of contraction induced by LV free wall stimulation was characterized by an early mechanical activation of anterior and anterolateral regions (pacing site) and delayed activation of inferior/septal-inferior regions (opposite site). At control, high-frequency dyssynchronous LV activation did not cause significant changes in circumferential shortening and wall stress and limited systolic wall thickening, whereas, as a predictable response to higher heart rate and metabolic demand, myocardial flow and glucose uptake increased. After 21 days of incessant pacing, this picture changed dramatically. Systolic circumferential shortening and wall thickening were depressed markedly in both sites when the pacemaker was turned on. However, at spontaneous heart rate, the regional contractile impairment was more pronounced in the pacing site than in the opposite site; therefore, we expected analogous differences in wall stress. Interestingly, this was not the case, indicating that, in response to chronic dyssynchronous activation, LV wall compensates for differences in regional stress. Other authors have also found no regional wall stress differences by cardiac echocardiographic assessment in a similar model of pacing-induced HF (16). We can now provide a possible explanation for this phenomenon, based on MRI-aided analysis of LV regional function; considering Eq. 2 in MATERIALS AND METHODS, it is evident that wall stress will remain constant if reductions of thickness are compensated by consensual changes of ventricular radius in the corresponding LV region. In fact, we found an earlier systolic displacement of the pacing site toward the centroid (Figs. 1 and 2) that shortened the end-systolic radius, thus compensating for reduced wall thickening. Therefore, even at spontaneous heart rate, the pacing site maintained the “memory” of early activation and contraction, possibly because of electrical remodeling. Notably, a very recent study has shown changes in electrical conduction velocity associated with altered expression and distribution of differentially phosphorylated forms of connexin-43 during the development of pacing-induced HF (2).

Myocardial blood flow, assessed with positron-emitting ammonia, was globally reduced but better preserved in the pacing site. High-frequency stimulation failed to enhance it, suggesting an impaired reserve because of coronary microvascular dysfunction. The inability of coronary microcirculation to respond to various types of stress, including exercise, has been.
well documented by others in experimental and human dilated cardiomyopathy (10, 27, 41, 47). However, two additional methods for flow measurement, one based on Doppler and the other on MRI, revealed an interesting discrepancy. Although flow appeared to be reduced by PET, values measured in the left anterior descending artery by a Doppler flow probe did not display significant changes, in accord with prior flow data obtained in the left circumflex coronary artery of dogs with pacing-induced HF (23, 31, 37, 29), although Traverse et al. (47) found reduced flow measured by Doppler in the same model of failure. Furthermore, the semiquantitative assessment with MRI evidenced a higher perfusion of the opposite site relative to the pacing site, consistent with microsphere-based measurements previously reported in LV-paced pigs (16). A possible explanation for such incongruities is that Doppler and microspheres or gadolinium provide a measure of instantaneous blood transit through a large conduit vessel or of first pass through cardiac microvessels, whereas PET determinations are based on the much more complex kinetics of a diffusible tracer such as \(^{13}\text{N}\)ammonia. Myocardial accumulation of this tracer depends not only on blood flow but also on its diffusion to parenchyma, transport across the cardiomyocyte membrane, and on ATP-consuming synthesis of ammonia and glutamate to form glutamine. Therefore, as pointed out by a number of investigators (19, 21), myocardial extraction and retention of \(^{13}\text{N}\)ammonia provides a combined estimate of blood flowing through the myocytes and cellular viability, which includes the capacity to generate energy, notoriously impaired in the failing heart. It is noteworthy that the marked reduction in myocardial flow revealed by PET in pacing-induced HF is similar to that found in previous studies, including our own, that applied the same type of diagnostic imaging to HF patients (20, 26).

After 21 days of pacing, an alteration in cardiac metabolism, which was partially suggested by reduced \(^{13}\text{N}\)ammonia accumulation, was clearly indicated by increased \(^{18}\text{F}\)-deoxyglucose uptake. During fasting, the normal heart relies minimally on glucose as an energy substrate. Conversely, besides a depressed energy production, the failing myocardium displays a fall in free fatty acid oxidation and a marked increase in glucose utilization (45) that, in the case of pacing-induced HF, can be \(>150\%\) of control (12, 31, 37). The pathophysiological significance of this metabolic alteration is still debated; however, we have provided solid evidence suggesting that it might significantly contribute to oxidative stress (15), a recognized cause of progressive myocardial damage during the evolution of HF (11). Therefore, for a better understanding of the evolution of cardiac failure, it is important to determine...
whether regional alterations in function and glucose utilization follow a similar pattern. We did not find a strict correlation on a regional basis. PET-measured cardiac glucose uptake was markedly and homogeneously augmented in HF, similar to previous findings in patients with dilated cardiomyopathy (12) and did not further increase in response to pacing stress, indicating a metabolic rigidity. Moreover, in the present study, PET allowed the quantification of glucose uptake in the same regions of the heart selected for detailed assessment of flow, contractile function, and stress. It is evident that changes in glucose uptake seemed to parallel the uniform increase in wall stress rather than the asymmetric contractile and flow impairment. Of note, plasma insulin concentration was significantly higher in HF compared with control after overnight fasting, in accord with previous data obtained by other authors in dogs with pacing-induced HF (30). It is possible that elevated basal insulin could have contributed to the increased cardiac glucose uptake, although Nikolaidis et al. (30) found insulin resistance in HF dogs, and, as pointed out by them and on the basis of previous findings at molecular level (31), it is more likely that the switch to higher glucose utilization follows the downregulation of the fatty acid oxidative pathway.

At least two limitations of our study should be pointed out. First, we used gadolinium-delayed contrast-enhanced images as a noninvasive index of tissue fibrosis, although a more precise assessment would have required histological analysis. Other authors, however, have found that, despite induction of procollagen, 3 wk of high-frequency pacing did not cause detectable myocardial fibrosis in pigs (1, 43). Second, 18F-deoxyglucose allowed us to measure glucose uptake, but not the rate of oxidative and nonoxidative glycolysis. Therefore, we could not determine whether coronary flow alterations enhanced lactate production in the failing heart. In a previous study (31), however, by employing the tracers [14C]glucose and [13C]lactate, we found no significant changes in lactate release after development of pacing-induced HF.

In conclusion, high-frequency pacing of the LV free wall causes a dysynchronous pattern of activation that leads to progressive cardiac failure with pronounced differences in regional contractility and flow but global abnormalities in myocardial metabolism. Taken together, our data indicate that the nonuniform functional derangement consequent to chronic dysynchronous contraction is not necessarily linked to disparities in metabolic alterations.

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