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TRANSLATIONAL PHYSIOLOGY |

Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy

Danilo Neglia,¹ Alberto De Caterina,³ Paolo Marraccini,¹ Andrea Natali,² Marco Ciardetti,¹ Cecilia Vecoli,³ Amalia Gastaldelli,¹ Demetrio Ciociaro,¹ Paola Pellegrini,¹ Roberto Testa,¹ Luca Menichetti,¹ Antonio L'Abbate,^{1,3} William C. Stanley,³ and Fabio A. Recchia^{3,4}

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Neglia D, De Caterina A, Marraccini P, Natali A, Ciardetti M, Vecoli C, Gastaldelli A, Ciociaro D, Pellegrini P, Testa R, Menichetti L, L'Abbate A, Stanley WC, Recchia FA. Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol* 293: H3270–H3278, 2007. First published October 5, 2007; doi:10.1152/ajpheart.00887.2007.—Under resting conditions, the failing heart shifts fuel use toward greater glucose and lower free fatty acid (FFA) oxidation. We hypothesized that chronic metabolic abnormalities in patients with dilated cardiomyopathy (DCM) are associated with the absence of the normal increase in myocardial glucose uptake and maintenance of cardiac mechanical efficiency in response to pacing stress. In 10 DCM patients and 6 control subjects, we measured coronary flow by intravascular ultrasonometry and sampled arterial and coronary sinus blood. Myocardial metabolism was determined at baseline, during atrial pacing at 130 beats/min, and at 15 min of recovery by infusion of [³H]oleate and [¹³C]lactate and measurement of transmucosal arteriovenous differences of oxygen and metabolites. At baseline, DCM patients showed depressed coronary flow, reduced uptake and oxidation of FFA, and preferential utilization of carbohydrates. During pacing, glucose uptake increased by 106% in control subjects but did not change from baseline in DCM patients. Lactate release increased by 122% in DCM patients but not in control subjects. Cardiac mechanical efficiency in DCM patients was not different compared with control subjects at baseline but was 34% lower during stress. Fatty acid uptake and oxidation did not change with pacing in either group. Our results show that in DCM there is preferential utilization of carbohydrates, which is associated with reduced flow and oxygen consumption at rest and an impaired ability to increase glucose uptake during stress. These metabolic abnormalities might contribute to progressive cardiac deterioration and represent a target for therapeutic strategies aimed at modulating cardiac substrate utilization.

microcirculation

FATTY ACIDS provide 60–90% of the energy necessary to sustain contractile function in the resting fasting state, with the remainder coming from glucose and lactate oxidation. During acute cardiac stress, such as pacing or exercise, the healthy human heart rapidly increases glucose and lactate uptake, with a relative decline in free fatty acid (FFA) uptake (1, 3, 4, 9). Clinical and animal studies have suggested that this response is

advantageous: it increases myocardial metabolic efficiency, since carbohydrates are a more efficient substrate than lipids, generating more contractile power for any given rate of myocardial oxygen consumption ($\dot{M}\dot{V}O_2$) (20, 29, 31).

Dilated cardiomyopathy (DCM) is often characterized by reduced FFA uptake and oxidation and accelerated glycolysis and glucose oxidation under resting conditions (7, 21, 31). This metabolic shift may act to optimize the limited oxidative capacity of cardiomyopathic hearts resulting from impairment of mitochondrial function (28) and/or ATP transfer from mitochondria to the contractile apparatus (30) or reduced myocardial perfusion and flow reserve due to coronary microvascular dysfunction (16, 17). Little is known about myocardial metabolism in DCM patient under conditions of increased workload. Factors that differentiate DCM from healthy conditions (altered metabolic phenotype, limited oxidative capabilities, reduced flow availability, etc.) might limit the ability of the dysfunctional myocardium to adapt to acute stress. The myocardial metabolic and flow response to acute atrial pacing stress has been extensively investigated in patients with syndrome X (1, 3) and coronary artery disease (23, 24, 39) but not in DCM patients. This information is clinically relevant, since metabolic modulators, such as agents that partially inhibit myocardial FFA oxidation, improve symptoms of stress-induced ischemia in angina patients (32) and ventricular function in patients with ischemic cardiomyopathy (2, 13, 31, 37), but the rationale for their potential use in heart failure and DCM is still under debate.

The purpose of the present investigation was to assess the relationships among cardiac substrate metabolism, ventricular dysfunction, and coronary blood flow (CBF) at rest and in response to acute pacing stress in DCM patients and in a control group of patients with normal coronary arteries and left ventricular (LV) mass and volume. We hypothesized that the chronic metabolic abnormalities in DCM observed at rest are associated with the absence of the normal response to pacing stress, namely, an increase in myocardial glucose uptake and maintenance of cardiac mechanical efficiency. Coronary hemodynamics and myocardial substrate metabolism were measured directly by cardiac catheterization and transmucosal

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blood sampling using an infusion of [³H]oleate and [¹³C]lactate tracers.

MATERIALS AND METHODS

Study Population

From October 2003 to May 2006, we enrolled 10 consecutive patients with DCM and 6 patients with normal LV function (controls), which were selected among the 329 patients admitted to the cardiology unit of the Institute of Clinical Physiology in Pisa, Italy, and showed normal coronary arteries with angiography. DCM patients were selected according to the following inclusion criteria: age between 20 and 80 yr, LV ejection fraction (EF) <40%, LV end-diastolic diameter (LVEDD) >56 mm, and angiographically normal coronary arteries (<50% coronary diameter stenosis). Exclusion criteria were as follows: New York Heart Association (NYHA) class IV, previous myocardial infarction, valvular heart disease, actual systemic arterial hypertension, myocardial active inflammatory/infective diseases (such as myocarditis or pericarditis), current cigarette smoking, diabetes, or the presence of other systemic illnesses (such as neoplasia, renal, hepatic, or respiratory failure or atrial fibrillation). Control patients underwent coronary angiography for history of angina-like chest pain and/or previous stress tests suspicious for myocardial ischemia. Inclusion criteria for control patients were as follows: age between 20 and 80 yr, LV EF >50%, LVEDD <56 mm, angiographically normal coronary arteries (<50% coronary diameter reduction), and the absence of other cardiovascular or systemic diseases.

Both groups of patients underwent routine blood tests, ECG, chest X-ray, and resting two-dimensional echocardiogram. LV function, dimension, and mass were evaluated from two-dimensional echocardiogram data according to standardized protocols (12). Eight DCM patients were also submitted, within 30 days after the catheterization procedure, to PET with [¹³N]ammonia to measure the specific blood flow per gram of myocardial tissue ($\text{ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$) at rest. Specific flow was computed according to standardized protocols (17) in the left anterior descending coronary artery (LAD) myocardial territory (5).

The study was approved by the local ethical committee and conformed to the Declaration of Helsinki on human research, and written informed consent was obtained on the day before cardiac catheterization after complete explanation of the protocol and potential risks. All coronary-active drugs, including nitrates, Ca^{2+} antagonists, β -blockers, angiotensin-converting enzyme inhibitors, or statins, were suspended at least 24 h before catheterization.

Cardiac Catheterization

In the morning, after an overnight fast, all patients were submitted to routine coronary angiography and definitively enrolled after excluding the presence of significant coronary stenosis.

Cardiac catheterization was performed to measure coronary perfusion pressure, flow velocity, and cross-sectional area in the proximal third of the LAD and transmural arteriovenous gradients across the LAD myocardial territory of labeled ($[\text{L-3-}^{13}\text{C}]$ lactate and $[\text{9,10-}^3\text{H}]$ oleate) and nonlabeled substrates (FFA, glucose, and lactate). At the completion of diagnostic catheterization, an intravenous bolus of 110 mg $[\text{L-3-}^{13}\text{C}]$ lactate was administered, followed by an intravenous continuous infusion of $[\text{9,10-}^3\text{H}]$ oleate at 84 $\mu\text{Ci/h}$ and $[\text{L-3-}^{13}\text{C}]$ lactate at 130 mg/h , allowing a 30-min equilibration period. The [¹³C]lactate tracer was used to measure the simultaneous lactate uptake and efflux from the myocardium (8, 9, 39), and the [³H]oleate tracer was used to measure FFA oxidation from the myocardial production of ³H₂O (21). A 6-Fr guiding catheter was placed in the left main coronary ostium through a 7-Fr femoral artery introducer. An intracoronary heparin bolus (100 U/Kg) was given, and a 0.014-in. Doppler flow wire (FloWire, Volcano) was advanced into the LAD. A 2.9-Fr, 10-MHz intravascular ultrasound (IVUS) catheter (Eagle Eye Gold, Volcano) was passed over the flow wire and positioned in the

LAD coronary artery immediately distal to the first septal perforating branch. The Doppler flow wire was positioned 2 cm distal to the tip of the IVUS catheter to avoid artifacts caused by the catheter wake. The positions of the IVUS catheter and flow wire were documented by angiography and maintained throughout the study by fluoroscopic control. After LAD instrumentation, a 5-Fr catheter was advanced into the coronary sinus, up to the great cardiac vein, to withdraw venous blood from the LAD territory, and a unipolar pacing catheter was then positioned into the right atrium. Due to the complexity of the instrumentation, five additional patients, fulfilling the inclusion criteria but in whom the catheterization procedures could not be completed, were excluded from the study.

After calibration, phasic and mean coronary perfusion pressure (from the guiding catheter) and coronary flow velocity signals were continuously recorded on paper and acquired, together with ECG (leads DI-DII-DIII), on a personal computer equipped with dedicated software. IVUS images were obtained for ≥ 30 s at each step of the protocol, with temporal synchronization with flow velocity signals, and recorded for off-line analysis.

At each step of the protocol, arterial and venous blood samples were withdrawn simultaneously, over 30 s, from the femoral artery introducer and great cardiac vein and immediately processed for gas analysis and measurements of metabolite concentrations.

Study Protocol

The study protocol consisted of four steps. After the instrumentation was completed (~30 min), continuous monitoring of coronary hemodynamic signals was started and the baseline arteriovenous sampling was performed ("Baseline"). Heart rate was increased by atrial pacing to 110 beats/min for 3 min and to 130 beats/min for 3 additional min, and arteriovenous sampling was repeated ("Pacing"). Pacing was then stopped, and, 15 min later, a third pair of arteriovenous samples was withdrawn ("Recovery"). After an additional 15 min, when all hemodynamic parameters had returned to baseline, an intravenous adenosine infusion was given for 3 min unless it was not clinically tolerated or significant bradycardia (HR < 50 beats/min) or hypotension (systolic pressure < 90 mmHg) occurred. Coronary parameters were acquired at the end of the third minute of adenosine administration, or just before suspension, and were used to estimate coronary flow reserve.

Data Analysis

Coronary flow. Coronary flow was calculated offline by multiplying Doppler-derived mean flow velocity by coronary lumen cross-sectional area as measured by IVUS as described in the Data Supplement.¹

Coronary flow reserve was computed as adenosine/resting CBF. An estimate of myocardial mechanical efficiency was obtained from the rate-pressure product (RPP) and $\dot{M}\dot{V}\text{O}_2$ measured at each step as follows (see also the Data Supplement):

$$(\text{RPP}/\text{LV mass})/[\dot{M}\dot{V}\text{O}_2/(0.54 \times \text{LV mass})] = (\text{RPP} \times 0.54)/\dot{M}\dot{V}\text{O}_2$$

Metabolites. Blood samples from the femoral artery and coronary sinus were withdrawn slowly to avoid hemolysis and potential contamination with right atrial blood. The first 5 ml from the coronary sinus catheter were discarded to avoid contamination from either saline or blood present in the catheter. Oxygen consumption and metabolite uptake and oxidation were measured as previously described (9, 10, 26) (see Data Supplement). The percent $\dot{M}\dot{V}\text{O}_2$ due to FFA or lactate oxidation was calculated as previously described (26). For lactate, it was assumed that 100% of the [¹³C]lactate taken up by the heart was oxidized to CO₂ (9).

¹ Supplemental material for this article is available online at the *American Journal of Physiology-Heart and Circulatory Physiology* website.

Statistics. Data are presented as means \pm SE. Differences among patient groups for discrete clinical variables were evaluated by χ^2 -test. Coronary hemodynamic and metabolic data were compared in each study condition among groups and for different study conditions in the same group by two-way ANOVA followed by Fisher's exact test. An unpaired *t*-test was used to compare single study conditions between groups when appropriate. *P* values of <0.05 were considered significant.

RESULTS

Characteristics of the Study Population

Clinical, functional, and biohumoral data are shown in Table 1. The two groups did not significantly differ in age or sex. History of angina-like chest pain was more frequent in controls, whereas risk factors were similar in the two groups. Body mass index and the ratio of total triglycerides over HDL-cholesterol (surrogate measures of insulin resistance and metabolic syndrome) did not differ between the two groups. DCM patients showed reduced LV systolic function and an enlarged LV chamber, frequent left bundle branch block, and higher brain natriuretic peptide (BNP) and NH₂-terminal pro-BNP plasma levels. However, DCM patients did not show evidence of advanced heart failure (8 of 10 patients in NYHA classes I and II) or extensive sympathetic activation (norepinephrine plasma levels were not significantly different between DCM

Table 1. Clinical, functional, and biohumoral data

	Controls	DCM Patients	<i>P</i> Values
Subject characteristics			
<i>n</i>	6	10	
Age, yr	67 \pm 2	57 \pm 3	NS
Males	3 (30)	7 (70)	NS
Angina	5 (83)	2 (20)	<0.05
Left branch bundle block	2 (33)	9 (90)	<0.05
LV mass, g	164 \pm 11	287 \pm 19	<0.01
New York Heart Association class III	0	2 (20)	NS
Functional data			
LV EF, %	58 \pm 1	32 \pm 1	<0.001
LVEDD, mm	49 \pm 1	65 \pm 1	<0.001
Neurohormonal data			
BNP, pg/ml	21 \pm 7	91 \pm 22	<0.05
NH ₂ -terminal pro-BNP, pg/ml	123 \pm 37	593 \pm 130	<0.05
Norepinephrine, pg/ml	210 \pm 54	412 \pm 81	NS
Risk factors			
Body mass index, kg/m ²	28 \pm 2	29 \pm 2	NS
Fasting glycemia, mg/dl	90 \pm 4	101 \pm 9	NS
Total triglycerides/HDL-cholesterol	2.79 \pm 1.73	3.07 \pm 2.71	NS
HDL/total cholesterol	0.23 \pm 0.02	0.24 \pm 0.02	NS
Treatment			
Statins	3 (50)	3 (30)	NS
Antiplatelet	2 (33)	5 (50)	NS
Ca ²⁺ antagonists	1 (17)	0	NS
β -Blockers (carvedilol)	3 (50)	6 (60)	NS
Angiotensin-converting enzyme inhibitors/angiotensin type 1 receptor antagonists	3 (50)	9 (90)	NS
Antialdosteronics	0	3 (30)	NS
Diuretics	1 (17)	8 (80)	<0.05
Digoxin	0	5 (50)	<0.05

Values are means \pm SE and are numbers of subjects (*n*) with percentages in parentheses unless otherwise stated. DCM, dilated cardiomyopathy; LV, left ventricular; EF, ejection fraction; LVEDD, LV end-diastolic diameter; BNP, brain natriuretic peptide; NS, not significant.

Table 2. Hemodynamics

	Controls	DCM Patients
Heart rate, beats/min		
Baseline	75 \pm 5	71 \pm 4 ^a
Pacing	132 \pm 4 ^e	124 \pm 4 ^{a,e}
Recovery	77 \pm 7	71 \pm 4 ^a
Mean aortic pressure, mmHg		
Baseline	107 \pm 2	89 \pm 3 ^b
Pacing	109 \pm 3 ^c	91 \pm 4 ^{b,c}
Recovery	105 \pm 4	90 \pm 4 ^b
Rate-pressure product, mmHg \cdot beats \cdot min ⁻¹		
Baseline	8,086 \pm 590	6,320 \pm 413 ^b
Pacing	14,475 \pm 642 ^e	11,314 \pm 647 ^{b,e}
Recovery	8,155 \pm 870	6,438 \pm 440 ^b
Left anterior descending coronary artery CBF, ml \cdot min ⁻¹ \cdot g ⁻¹		
Baseline	1.08 \pm 0.07	0.66 \pm 0.06 ^b
Pacing	1.19 \pm 0.07 ^c	0.91 \pm 0.07 ^{b,d}
Recovery	0.84 \pm 0.04 ^f	0.64 \pm 0.07 ^b

Values are means \pm SE. CBF, coronary blood flow. ^a*P* = NS, DCM patients vs. controls; ^b*P* < 0.001 , DCM patients vs. controls; ^c*P* = NS, pacing vs. baseline and recovery; ^d*P* < 0.01 , pacing vs. baseline and recovery; ^e*P* < 0.001 , pacing vs. baseline and recovery; ^f*P* < 0.05 , recovery vs. baseline and pacing.

patients and controls). Use of primary cardioactive drugs was not significantly different between the two groups except for digoxin and diuretics in DCM patients.

Coronary Hemodynamics

In one patient in the control group, the coronary sinus catheter was displaced into the right atrium; thus, metabolic measurements were not obtained. In two patients of the DCM group, the pacing rate was maintained at 110 beats/min since they did not tolerate higher rates; in one of these two patients and in one other patient, intravenous adenosine was not administered as they asked to shorten the study.

Data on coronary hemodynamics during and after pacing stress are shown in Table 2. While heart rates were not significantly different between controls and DCM patients, coronary mean perfusion pressure, RPP, and CBF in the LAD territory were lower in DCM patients than in controls under all the study conditions. From baseline to pacing, heart rates and RPP significantly increased in both groups and were restored to baseline levels at recovery. CBF significantly increased during pacing only in the DCM group and significantly decreased at recovery in the control group.

During intravenous adenosine infusion, there was a trend for CBF to remain lower in DCM patients than in controls (2.18 \pm 1.30 vs 3.29 \pm 0.89 ml \cdot min⁻¹ \cdot g⁻¹, *P* = 0.09), whereas the coronary flow reserve was not significantly different between the two groups (3.59 \pm 2.53 vs 3.31 \pm 1.25, not significant).

Myocardial Metabolism and Energetics

Baseline arterial concentrations of the major cardiac substrates were not significantly different between the two groups (Table 3) and did not significantly change during the study. DCM patients showed significantly lower FFA uptake and oxidation at all time points and significantly higher glucose uptake than controls at baseline (Fig. 1). During pacing, glucose uptake significantly increased in controls by 106% but did

Table 3. Arterial concentration of substrates

	Controls	DCM Patients	P Values
FFA	1.93±0.21	1.34±0.18	NS
Glucose	5.45±0.09	5.37±0.31	NS
Lactate	0.51±0.03	0.61±0.08	NS

Values are means ± SE (in μmol/ml). FFA, free fatty acids.

not change in DCM patients, so that it was no longer different between the two groups. The percent net extraction of arterial FFA was unaffected by pacing and was similar between groups (Table 4). On the other hand, glucose and lactate extraction were higher in the DCM group than in the control group. Glucose extraction did not significantly increase during pacing stress in controls but decreased significantly in DCM patients compared with baseline and recovery periods (Table 4).

The tracer-measured myocardial uptake of lactate was not significantly different between controls and DCM patients at baseline and did not show significant changes during stress in both groups (Fig. 2). At recovery, it significantly decreased in controls. Myocardial lactate release was significantly lower in DCM patients than in controls at baseline, but during pacing it significantly increased by 122% in DCM patients and reached levels similar to controls. Net uptake tended to be higher in DCM patients, but this difference was not statistically significant.

Overall, RPP and $\dot{M}V_{O_2}$ were lower in DCM patients than in controls (Fig. 3). However, the ratio of RPP to $\dot{M}V_{O_2}$ (an index of myocardial mechanical efficiency, i.e., work performed for a given amount of oxygen consumed) was significantly lower in DCM patients only during stress and at recovery. In fact, during pacing, RPP increased in both groups, but $\dot{M}V_{O_2}$ increased only in DCM patients. At recovery, RPP returned to baseline in both groups, but in controls $\dot{M}V_{O_2}$ declined below baseline levels. The analysis of the percent $\dot{M}V_{O_2}$ due to oxidation of FFA showed that FFA contributed more to $\dot{M}V_{O_2}$ in controls than in DCM patients and that this difference was attenuated during pacing stress (Fig. 4, top). While the contribution of lactate oxidation to $\dot{M}V_{O_2}$ tended to be greater in DCM patients than in controls, this difference did not reach statistical significance (Fig. 4, bottom).

Correlations Between LV Remodeling and Metabolism, Energetics, and CBF

There was a strong inverse correlation between LV diameter (an index of LV dysfunction/remodeling) and CBF, $\dot{M}V_{O_2}$, and FFA uptake in the whole study population under basal conditions (Fig. 5). There was a nonsignificant trend toward a positive correlation with glucose uptake ($r = 0.41$, not significant). Both under resting conditions and during pacing, FFA uptake (but not glucose uptake) was directly related with $\dot{M}V_{O_2}$ (Fig. 6).

DISCUSSION

This study provides direct evidence for a chronic cardiac metabolic shift under both resting conditions and with pacing stress in DCM patients without advanced heart failure. This change in cardiac metabolic profile was characterized by decreased FFA uptake and oxidation and increased carbohydrate

utilization and was associated with reduced cardiac work, $\dot{M}V_{O_2}$, and myocardial blood flow both at rest and in response to stress. These results suggest the novel view that, while the switch away from FFA oxidation in the failing heart is thought to be compensatory under resting conditions, it may be detrimental during even moderate stress, potentially contributing to the progressive deterioration of myocardial function.

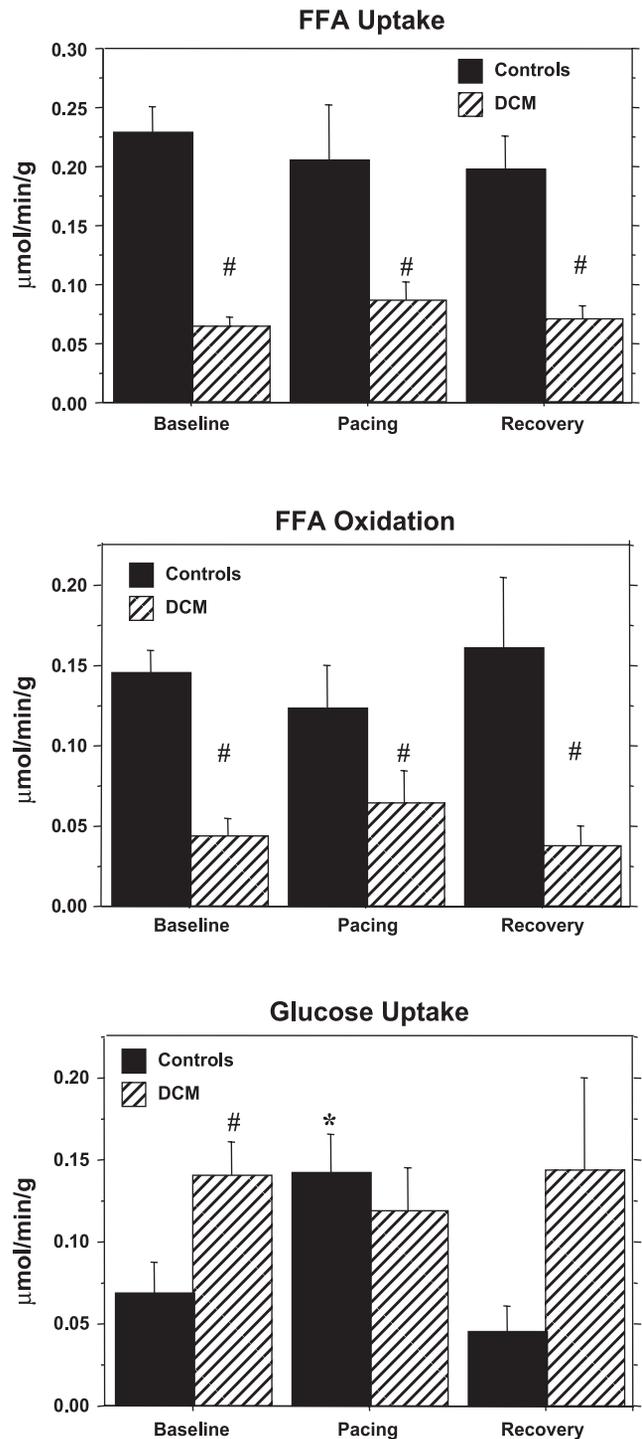


Fig. 1. Cardiac free fatty acid (FFA) uptake (top), FFA oxidation (middle), and glucose uptake (bottom) in controls (n = 5) and DCM patients (n = 10) at baseline, during atrial pacing, and at recovery. *P < 0.05, pacing vs. baseline and recovery; #P < 0.05, DCM patients vs. controls.

Table 4. Percent transmyocardial net extraction of arterial FFA, glucose, and lactate

	Controls	DCM Patients	P Value
FFA extraction			
Baseline	15±5	18±10	NS
Pacing	12±5	15±8	NS
Recovery	17±6	19±12	NS
Glucose extraction			
Baseline	1±1	4±2†	<0.05
Pacing	2±1	2±2*†	NS
Recovery	1±1	5±7†	NS
Lactate extraction			
Baseline	18±14	32±11‡	NS
Pacing	17±12	27±11‡	NS
Recovery	9±8	29±16‡	<0.05

Values are means ± SE (in %). P values are DCM patients versus controls under the given conditions. * $P < 0.05$ compared with baseline and recovery; † $P < 0.05$, DCM patients vs. control for main effect; ‡ $P < 0.001$, DCM patients vs. controls for main effect.

Previous studies in patients with cardiomyopathy/heart failure have yielded conflicting results. Noninvasive PET studies in nonischemic cardiomyopathy found reduced uptake and oxidation of [^{11}C]palmitate (35) and/or increased uptake and utilization of [^{11}C]glucose (7), consistent with our direct invasive measurements. However, other PET studies, using FFA and glucose analogs in ischemic and nonischemic patients with advanced heart failure, found opposite results, with increased lipids and decreased carbohydrate uptake (33, 38). Paolisso et al. (22) evaluated myocardial energy metabolism in patients with heart failure by direct invasive measurement of transmyocardial substrate gradients and showed increased FFA utilization. However, this study enrolled patients with NYHA class II and III heart failure of ischemic and nonischemic origin and no labeled substrates were used. In the present study, patients were carefully selected to include only those with idiopathic DCM and without advanced heart failure to avoid the potential confounding effects of coronary disease and of systemic metabolic derangement associated with cardiac decompensation. In severe heart failure, elevated adrenergic stimulation may increase $\text{M}\dot{\text{V}}\text{O}_2$ and levels of FFA, and cardiac insulin resistance may develop (19). As a consequence, both fatty acid and glucose utilization may be altered, and a condition of energy imbalance may ensue, as recently discussed by Neubauer (18).

The resting metabolic pattern that we found in DCM is similar to that observed in the experimental model of pacing-induced cardiomyopathy (21, 25) and is consistent with findings in other animal models of progressive cardiac dysfunction and heart failure (11). This shift in myocardial substrate metabolism partially mimics the neonatal metabolic phenotype, with glucose and lactate instead of fatty acid being the primary energy substrate (31). It remains to be determined whether these alterations are a compensatory response of the failing heart that optimizes cardiac energy metabolism and prevents further deterioration of LV function or rather is a maladaptation that contributes to the progression toward decompensation. Insight on this issue comes from mice with cardiac-specific overexpression of insulin-independent glucose transporter 1, which have increased glucose uptake and less contractile dysfunction and LV dilation in response to chronic

pressure overload (15), suggesting that accelerated glucose metabolism prevents hypertension-induced heart failure.

We observed an inverse correlation between cardiac FFA metabolism and the extent of LV remodeling, which was also associated with reduced $\text{M}\dot{\text{V}}\text{O}_2$, myocardial blood flow, and

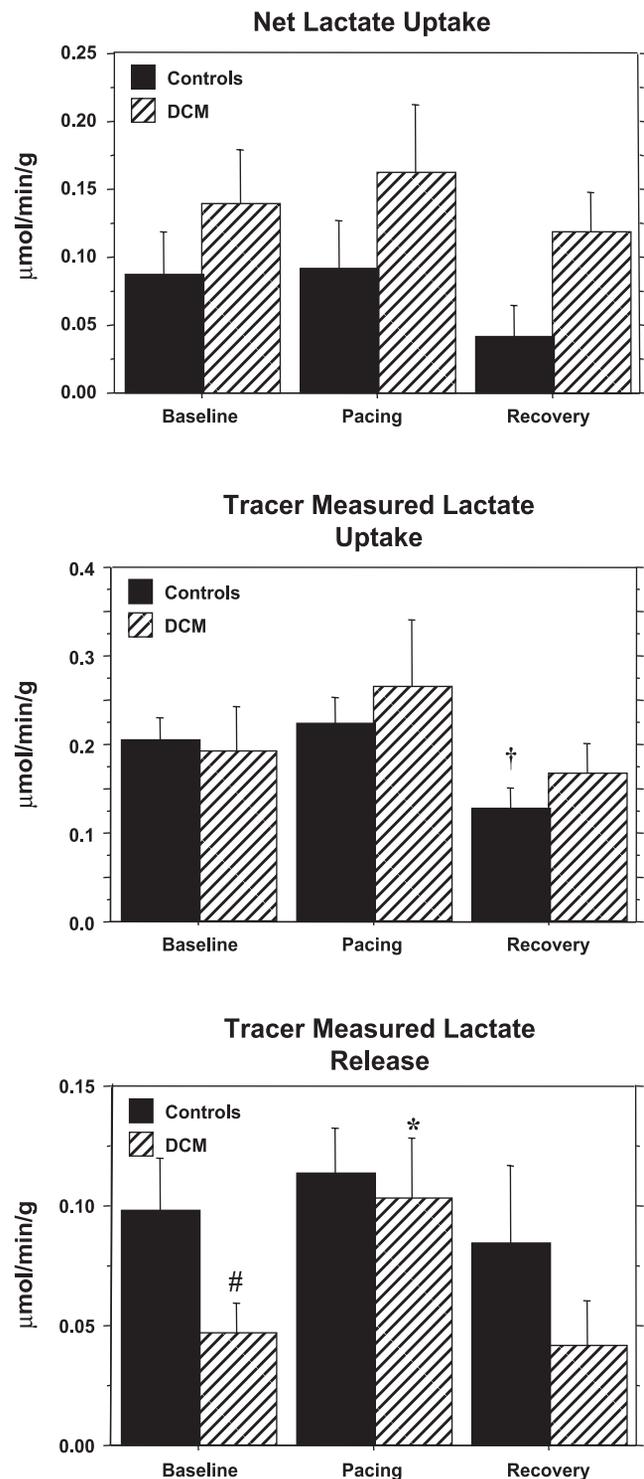


Fig. 2. Cardiac net lactate uptake (top) and tracer-measured lactate uptake (middle) and release (bottom) in controls ($n = 5$) and DCM patients ($n = 10$) at baseline, during atrial pacing, and at recovery. * $P < 0.05$, pacing vs. baseline and recovery; † $P < 0.05$, recovery vs. baseline and pacing. # $P < 0.05$, DCM patients vs. controls.

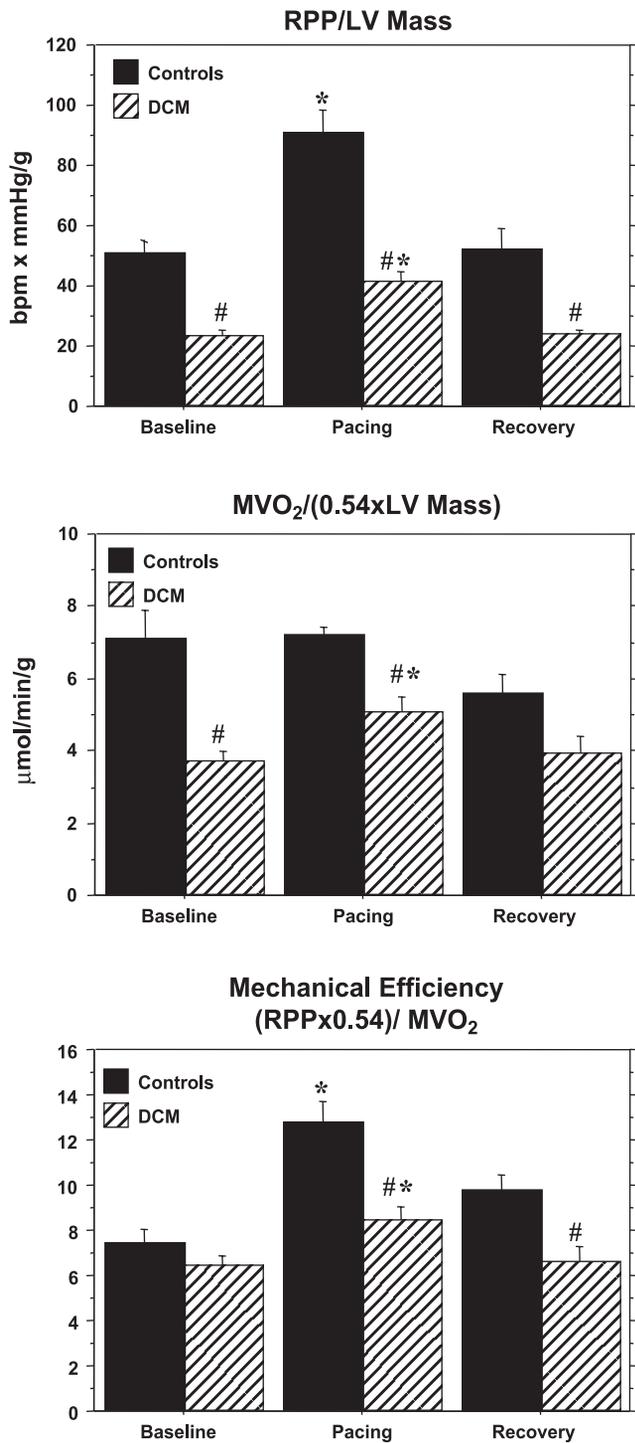


Fig. 3. Rate-pressure product [RPP; in mmHg·beats·min⁻¹ (bpm); top], an estimate of cardiac work, myocardial oxygen consumption (MVO₂; middle), and mechanical efficiency, estimated from the ratio between RPP and MVO₂ (bottom), in controls (n = 5) and DCM patients (n = 10) at baseline, during atrial pacing, and at recovery. All values were corrected for left ventricular (LV) myocardial mass. *P < 0.05, pacing vs. baseline and recovery; #P < 0.05, DCM patients vs. controls.

cardiac work. A primary depression of myocardial function, as can be expected in DCM, could cause reduced energy requirements and MVO₂ and consequently reduced blood flow with downregulation of FFA metabolism and a possible increase in

carbohydrate utilization. A reduction of myocardial oxygen availability due to impaired myocardial perfusion and coronary microvascular dysfunction (16, 17) and impaired oxygen utilization consequent to mitochondrial dysfunction (28) have been also described in DCM. These mechanisms reduce energy transduction and further impair contractility and could, by themselves, stimulate the myocardial metabolic shift from fat oxidation to preferential utilization of carbohydrates. On the other hand, a primary metabolic abnormality could exist, with lower activity of the β-oxidation pathway (27), lowering MVO₂ and causing metabolic downregulation of coronary flow, but also energy depletion and reduced contractile function.

Myocardial Metabolic Response to Stress in DCM

The myocardial metabolic response to stress in DCM patients had not previously been investigated. It is well established that in normal hearts, a high rate pacing induces a rapid increase in glucose and lactate uptake coupled with a relative decline in FFA uptake (1, 3, 4, 9). Clinical and experimental studies have suggested that this response is advantageous, since it increases myocardial mechanical efficiency as carbohydrates are a more efficient substrate than lipids and provides more energy for the generation of contractile power for any given MVO₂ (20, 29, 31). The response to pacing stress in

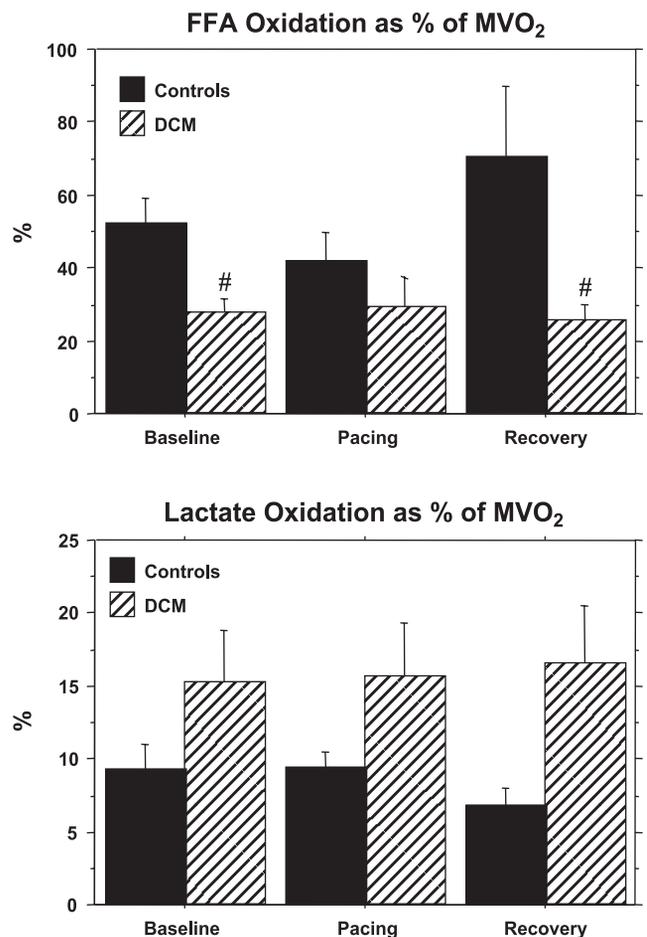


Fig. 4. Percent contribution of FFA oxidation (top) or lactate oxidation (bottom) to MVO₂ in controls (n = 5) and DCM patients (n = 10) at baseline, during atrial pacing, and at recovery. #P < 0.05, DCM patients vs. controls.

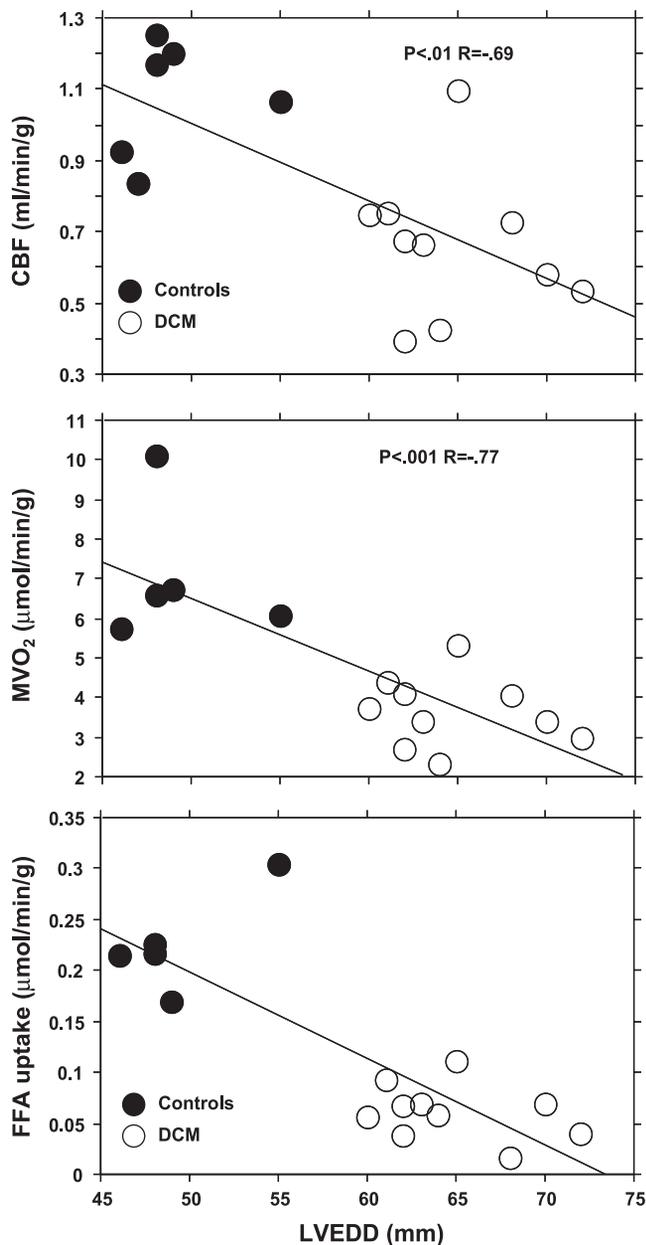


Fig. 5. Correlations between LV end-diastolic diameter (LVEDD) and resting coronary blood flow (CBF; *top*), MVO₂ (*middle*), and myocardial FFA uptake (*bottom*) in controls and DCM patients.

DCM patients was very different from the control group: glucose uptake, which at baseline was already elevated in DCM patients to levels similar to those reached in controls during stress, did not further increase. In contrast, FFA utilization tended to increase and the relative contribution of lipid oxidation to MVO₂, which was clearly lower in DCM patients than in controls under resting conditions, became similar between the two groups during stress. Compared with controls, there was a lower increase in myocardial mechanical efficiency during pacing in DCM patients. Taken together, these findings strongly indicate that there is a more limited cardiac metabolic reserve and flexibility in DCM. One of the possible mechanisms explaining the metabolic rigidity of the failing heart is the paradoxical downregulation of key enzymes of the carbo-

hydrate oxidative pathway, despite the higher glucose oxidation, which we have previously described in dogs (14). As a consequence, the cardiomyopathic heart must face even moderate increases in cardiac work by oxidizing less efficient substrates, such as FFA, which require higher oxygen consumption and blood flow.

This abnormal metabolic behaviour, together with impaired mitochondrial function (28) and limited myocardial flow and oxygen availability, possibly due to coronary microvascular dysfunction (16, 17), could contribute to an ischemic-like condition (6, 36), enhanced oxidative stress, and energy depletion in the cardiomyopathic heart.

Study Limitations

The small number of both DCM and control patients, due to the strict selection criteria and the complexity of the protocol, limits the statistical power. A second limitation is the lack of a completely normal control population. Control patients had a history of angina-like chest pain and/or stress testing suggestive for ischemia. However, neither group of patients had the typical clinical and ECG pattern of syndrome X nor developed

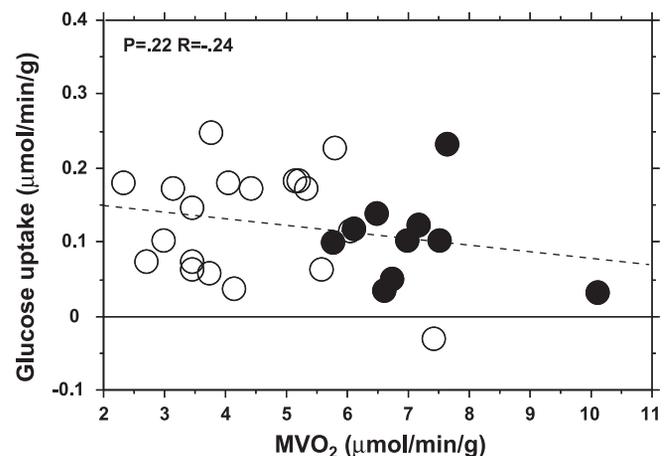
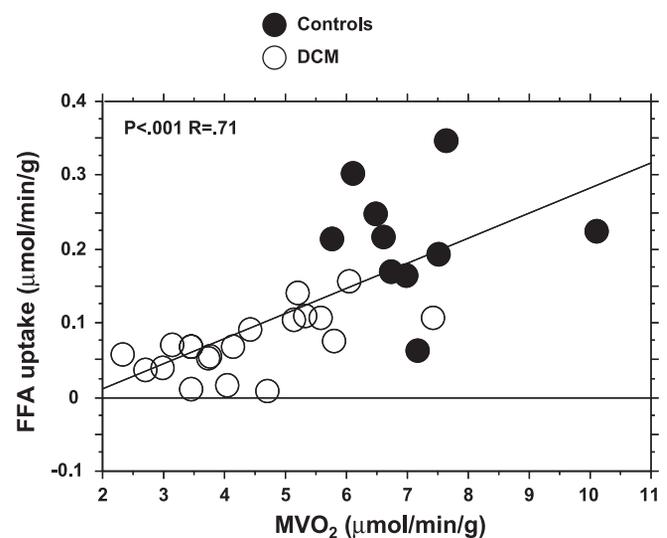


Fig. 6. Correlations between MVO₂ and myocardial FFA uptake (*top*) and glucose uptake (*bottom*) measured at rest and during pacing in controls and DCM patients.

chest pain or significant S-T segment depression during pacing stress. Since coronary catheterization procedures have an intrinsic risk to life, it is unethical to study a truly normal population.

Glucose oxidation was not measured because of the significant additional adsorbed radiation dose to the patient. It is important to know the effects of DCM and acute stress on glucose uptake and oxidation to CO₂ and release of lactate, which can only be assessed using [¹⁴C]glucose. While the present study is the first to assess myocardial lactate kinetics in DCM patients using [¹³C]lactate tracers, these experiments would be greatly strengthened by dual-isotopic studies using [¹⁴C]glucose/[¹³C]lactate tracers, as previously described (9, 39). Another limitation in the metabolic measurements is the inability to measure the oxidation of intracardiac substrate stores (e.g., glycogen and triglycerides), which likely played an important role in supporting the increase in M \dot{V} O₂ in response to pacing in the DCM group (Fig. 3).

Diabetes was an exclusion criterion for enrolment of both DCM and control patients; however, it cannot be excluded that the two patient populations differ in insulin resistance, and that this could have influenced the metabolic response to stress. Oral glucose tolerance test was not performed, however, BMI and the triglycerides/HDL was similar between the two groups, suggesting that whole body metabolic abnormalities were similar.

According to the study protocol, pacing moderately increased heart rate to allow tolerability in DCM patients. This choice could have caused a relatively lower increase in cardiac workload in normal hearts than in cardiomyopathic hearts where the effects of heart rate on energy expenditure are added to those of enhanced wall stress. Due to the complexity of the protocol we could not measure ventricular volumes to have a better estimate of actual workload than that provided by RPP values. The somewhat artificial conditions of studying these patients in the catheterization laboratory and the use of heparin likely resulted in elevated FFA in both groups. Accordingly, baseline metabolic data should be extended with caution to what one would see in the unheparinized resting state. It would be best to use a more physiological stimulus to increase M \dot{V} O₂, such as exercise or high dose dobutamine infusion, however, these stresses are not feasible in instrumented patients with DCM prone to arrhythmias.

Conclusions

The present findings demonstrate that DCM patients have a shift in cardiac metabolism away from FFA oxidation both at rest and during pacing stress, which is associated with enlargement of the LV and reduced cardiac work, M \dot{V} O₂, and myocardial blood flow. In addition, these patients show a failure to further increase glucose uptake and possibly oxidative glycolysis in response to pacing stress. Our results suggest the novel view that, while the switch away from FFA oxidation in DCM hearts appears to be compensatory under resting conditions, it may be detrimental during even moderate stress, potentially contributing to progressive deterioration of myocardial function. These findings will better orient therapeutic strategies aimed at modulating mitochondrial substrate oxidation to reduce symptoms and improve cardiac performance in DCM patients (2, 13).

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