OBJECTIVES We investigated whether cardiac resynchronization therapy (CRT) affects myocardial glucose metabolism and perfusion in dilated cardiomyopathy (DCM) and left bundle branch block (LBBB).

BACKGROUND Patients with DCM and LBBB present with asynchronous left ventricular (LV) activation, leading to reduced septal glucose metabolism. Cardiac resynchronization therapy recoordinates LV activation, but its effects on myocardial glucose metabolism and perfusion remain unknown.

METHODS In 15 patients (10 females; 61 ± 13 years) with DCM and LBBB (QRS width 165 ± 15 ms), gated 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and technetium-99m (99mTc)-sestamibi single-photon emission computed tomography were performed before and after two weeks of CRT. Uptake of FDG and 99mTc-sestamibi was determined in four LV wall areas. Ejection fraction and volumes were calculated from gated PET.

RESULTS Baseline FDG uptake was heterogeneous (p < 0.0001), with lowest uptake in the septal region (56 ± 12%) and highest uptake in the lateral region (89 ± 6%). During CRT, septal and anterior increases (p < 0.01) and lateral decreases (p < 0.01) resulted in homogeneously distributed glucose metabolism. Baseline heterogeneity (p < 0.0001) in 99mTc-sestamibi uptake was modest (lowest septal 65 ± 10%; maximum lateral 84 ± 5%) and also reduced with CRT, although some heterogeneity (p < 0.05) remained. The septal-to-lateral ratio increased with CRT for FDG (0.62 ± 0.12 to 0.91 ± 0.26, p < 0.001) and 99mTc-sestamibi uptake (0.77 ± 0.13 to 0.85 ± 0.16, p < 0.01). The LV end-diastolic and end-systolic volumes decreased from 293 ± 160 to 272 ± 158 ml (p < 0.05) and from 244 ± 164 to 220 ± 160 ml (p < 0.01), respectively. Ejection fraction increased from 22 ± 12% to 25 ± 13% (p < 0.01).

CONCLUSIONS Glucose metabolism is reduced more than perfusion in the septal compared with LV lateral wall in patients with DCM and LBBB. Cardiac resynchronization therapy restores homogeneous myocardial glucose metabolism with less influence on perfusion. (J Am Coll Cardiol 2003;41:1523–8) © 2003 by the American College of Cardiology Foundation.
programmed atrioventricular delay was 105

Left ventricular pacing leads were positioned in a lateral

Coronary angiography. Patients received a resynchronization

Artery disease was ruled out in all patients by preoperative

QRS width of 165

Transmission

ine of relative FDG and 99mTc-sestamibi uptake values

uptake on the different myocardial wall areas (i.e., differ-

distribution elsewhere (11). Brieﬂy, emission was performed

and 15 min for transmission

Ungated FDG and 99mTc-sestamibi SPECT images, as well as

Visual vector sampling method in 25 segments. Segmental FDG

uptake values were assessed using a volumetric

Myocardial perfusion SPECT

SPECT

Myocardial perfusion SPECT

FDG Uptake and CRT

Patient with severe LV dilation due to nonischemic cardio-

FDG-PET. To reduce myocardial fatty acid metabolism

Stimulate insulin-dependent glucose uptake, all patients

Diluted cardiomyopathy

Fluorodeoxyglucose

Heart failure

Left bundle branch block

Left ventricular ejection fraction

Single-photon emission computed tomography

Technetium-99m

METHODS

Patients. We investigated 15 patients with DCM (10

women; age 61 ± 13 years; body weight 73 ± 14 kg) with

HF (all in New York Heart Association functional class III)

and LBBB. All patients were in sinus rhythm with a mean

PR interval of 200 ± 41 ms (range 165 to 310) and a mean

QRS width of 165 ± 15 ms (range 140 to 200). Coronary

artery disease was ruled out in all patients by preoperative

coronary angiography. Patients received a resynchronization

camcorder for biventricular pacing. Left ventricular pacing

leads were positioned in a lateral

position (n = 12) or anterolateral position (n = 3). The mean

programmed atrioventricular delay was 105 ± 17 ms.

Patients were examined with FDG-PET and 99mTc-

sestamibi SPECT immediately before and 14 days after

CRT initiation. They fasted on the study days and received

optimized medical HF treatment, which was unchanged

during the entire study.

The study was approved by the institutional Review

Committee, and patients gave written, informed consent to

participate in the trial.

FDG-PET. To reduce myocardial fatty acid metabolism

and stimulate insulin-dependent glucose uptake, all patients

received 250 mg acipimox 2 h and 50 g glucose orally 1 h

before administration of FDG. Gated FDG-PET scans

(ECAT EXACT 922/47, Siemens-CTI, Knoxville, Ten-

nessee) were performed 60 min after intravenous adminis-
	ration of 284 ± 30 MBq FDG, with eight gates per RR

interval. The acquisition time was 30 min for emission

(two-dimensional mode) and 15 min for transmission

(68Ge/68Ga rod sources). The eight sinograms of the gated

acquisition were added up to create one ungated sinogram,

and attenuation-corrected gated and ungated images were

reconstructed using an iterative algorithm (Ordered Subsets

Expectation Maximization [OSEM], 16 subsets, 6 steps).

For ungated and gated images, the matrix size was 128 ×

128 pixels and 64 × 64 pixels and the reconstruction zoom

was 2.15 and 1.78, respectively.

99mTc-sestamibi SPECT. Myocardial perfusion SPECT

imaging was performed 60 min after injection of 424 ± 17

MBq 99mTc-sestamibi, with a light meal after tracer appli-
cation. Data were acquired using a dual-head gamma

camera (Solus, ADAC Laboratories, Milpitas, California).

Acquisition parameters, attenuation- and scatter-corrected

reconstruction in a 128 × 128 matrix were described in
detail elsewhere (11). Brieﬂy, emission was performed

in three independent energy windows: 140 ± 14 keV for

emission, 120 ± 6 keV for scatter detection, and 90 ± 11

keV for backscatter detection. Data sets of windows 1 and 2

were processed to obtain a scatter-corrected data set, which

was then reconstructed using a Butterworth ﬁlter (cutoff

0.7 Nyquist, order of 5, matrix 128 × 128) and processed

with the data set of window 3 (ﬁltered backprojection, Ramp

0.5) to obtain a ﬁnal segmented attenuation- and scatter-
corrected transaxial data set.

PET and SPECT analyses. Ungated FDG and 99mTc-

sestamibi images were reoriented according to the LV axes.

Relative distributions of myocardial FDG and 99mTc-

sestamibi uptake values were assessed using a volumetric

vector sampling method in 25 segments. Segmental FDG

and 99mTc-sestamibi uptake was displayed as the percentage

of the segment with peak activity. Mean FDG and 99mTc-

sestamibi uptake of four LV wall areas (septal, anterior,

lateral, and posterior)—each consisting of six segments—

was calculated as the mean value of the respective six

segments for every patient. Due to possible ambiguous

assignment, the remaining apical segment was not included

in the wall area analysis. The septal-to-lateral ratios were

determined as septal FDG or 99mTc-sestamibi uptake di-

vided by the uptake values of the lateral wall. Figure 1

displays representative examples of FDG-PET and 99mTc-

sestamibi SPECT images, as well as individual uptake

values, at baseline and during CRT in a 50-year-old female

patient with severe LV dilation due to nonischemic cardio-

myopathy.

The pixel size of gated FDG images was changed to an

isotropic pixel size of 5.79 mm. These data were reoriented

and analyzed for LV end-diastolic (LVEDV) and end-
systolic volumes (LVESV), as well as for LVEF, with the

software tool called Quantitative Gated SPECT (QGS,

Cedars-Sinai Medical Center, California).

Statistics. Statistical analyses were performed using SPSS

version 10 (SPSS Inc., Chicago, Illinois). Data are ex-

pressed as the mean value ± SD. Dependencies of tracer

uptake on the different myocardial wall areas (i.e., differ-

ences of relative FDG and 99mTc-sestamibi uptake values

between septal, anterior, lateral, and posterior myocardium)

were analyzed using the nonparametric Kruskal-Wallis test.

This test was performed separately for both baseline and

CRT examinations. Differences between wall areas in their

responses over time, in terms of FDG or 99mTc-sestamibi

uptake values, were also assessed with the Kruskal-Wallis

test.

Intragroup comparisons (i.e., differences of mean values

before and during CRT) were tested for significance using a

nonparametric test for paired samples (Wilcoxon). Statisti-
analyses of differences between FDG and $^{99m}$Tc-sestamibi in their uptake values, septal-to-lateral ratios and corresponding changes over time were performed with a nonparametric test for independent samples (Mann-Whitney U test). A p value < 0.05 was considered significant.

RESULTS

Impact of CRT on myocardial glucose metabolism and perfusion. At baseline, glucose metabolism in patients with DCM and LBBB showed significant differences between the analyzed myocardial wall areas ($p < 0.0001$). Uptake was highest in the lateral wall and lowest in the septum, with intermediate values for the anterior and posterior wall (Fig. 2A). Myocardial perfusion also showed significant differences between the respective wall areas ($p < 0.0001$), although these were less marked than differences in glucose metabolism (Fig. 2B).

$^{99m}$Tc-sestamibi uptake was significantly higher than FDG uptake in the septum (65 ± 10% vs. 56 ± 12%, $p < 0.05$) and lower in the lateral wall (84 ± 5% vs. 89 ± 6%, $p < 0.01$). Accordingly, the mean septal-to-lateral ratio at baseline was significantly lower for FDG (0.62 ± 0.12) than for $^{99m}$Tc-sestamibi (0.77 ± 0.13, $p < 0.001$) (Figs. 2A and 2B).

During CRT, wall areas showed significantly different responses in their FDG uptake ($p < 0.0001$) and $^{99m}$Tc-sestamibi uptake ($p < 0.01$). Glucose metabolism increased significantly by 25% in the septum and 17% in the anterior wall, whereas metabolism decreased significantly by 11% in the lateral wall. Thus, glucose metabolism was homogeneously distributed in the LV myocardium and mean FDG uptake values did not differ between the respective wall areas ($p = 0.128$) (Fig. 2A). The influence of CRT on regional myocardial perfusion was less pronounced. Relative $^{99m}$Tc-sestamibi uptake increased by 6% in the septum and 8% in the anterior wall. A reduced spatial heterogeneity of myocardial perfusion between the respective wall areas ($p < 0.05$) remained, with lowest $^{99m}$Tc-sestamibi uptake in the septum and highest uptake in the lateral wall (Fig. 2B).

Consequently, mean septal-to-lateral ratios for FDG and $^{99m}$Tc-sestamibi both increased significantly to 0.91 ± 0.26 ($p < 0.001$) and 0.85 ± 0.16 ($p < 0.01$), respectively, although the relative increase was significantly ($p < 0.0001$) higher for FDG (47%) than for $^{99m}$Tc-sestamibi (10%) (Figs. 2A and 2B).

When the two patients with LV pacing were compared with the 13 patients paced in the biventricular mode, both baseline FDG and $^{99m}$Tc-sestamibi uptake values and changes during CRT were comparable between both pacing modes. Uptake values of FDG and $^{99m}$Tc-sestamibi before and during CRT in the two LV-paced patients were also substantively similar to those in all 15 patients.

Impact of CRT on LV function. At baseline, mean LVEDV and LVESV were 293 ± 160 and 244 ± 164 ml, respectively. After two weeks of CRT, LVEDV decreased significantly to 272 ± 158 ml ($p < 0.05$) and LVESV to 220 ± 160 ml ($p < 0.01$). Mean LVEF increased from 22 ± 12% at baseline to 25 ± 13% after CRT ($p < 0.01$).

DISCUSSION

Cardiac resynchronization therapy has been proposed as an adjunctive treatment for patients with severe HF and LBBB. Short-term hemodynamic (9,10,12) and long-term functional improvements have been reported (13–15). The benefit of CRT is achieved by improved chamber efficiency, as demonstrated by a reduction in myocardial energy consumption (16). Moreover, a reduction in LV volumes after...
CRT has been observed in echocardiographic studies (17,18).

Resynchronization of LV contraction by advancing LV free wall activation has been implicated as one major mechanism of CRT (19). The extent of the LV base displaying delayed longitudinal contraction, as detected by echocardiographic tissue Doppler imaging, has been shown to predict the long-term efficacy of CRT. With tissue tracking, improved regional longitudinal systolic shortening during CRT could be demonstrated (20). Near-simultaneous contraction of the septum and LV free wall may lead to septal reloading during LV systole. This is underscored by data provided by Kawaguchi et al. (21), who used contrast-enhanced echocardiography to show that one major mechanism of hemodynamic improvement with CRT is an increase in septal inward motion. With the same technique, these authors could also show a 40% reduction of LV dyssynchrony with CRT.

The main finding of our study is that the reduction of mechanical LV dyssynchrony by CRT is accompanied by homogenization of the unbalanced cardiac glucose metabolism in DCM and LBBB, with less influence on myocardial perfusion. Previous studies have shown a reduction in septal glucose metabolism in patients with LBBB (2,22). In contrast, results on resting perfusion abnormalities in LBBB have not uniformly demonstrated a reduction in septal perfusion (2,4–8,23). The results of our study indicate that septal glucose metabolism is more reduced than perfusion,

Figure 2. Mean (±SD) relative 18F-fluorodeoxyglucose (FDG) (A) and technetium-99m-sestamibi (B) uptake values of the four left ventricular wall areas, as well as septal-to-lateral ratios at baseline and during cardiac resynchronization therapy (CRT) in 15 patients. *p < 0.05, †p < 0.01, and ‡p < 0.001 compared with FDG.
which is in good agreement with the postulated septal reverse perfusion/glucose metabolism mismatch in LBBB (2,22).

The most likely explanation for reduced septal glucose uptake in LBBB is therefore a perfusion-independent specific alteration of transmembranous glucose transport and/or the subsequent phosphorylation kinetics (24). This is underscored by previous evidence for preserved septal viability and metabolic activity associated with beta-oxidation and oxygen consumption, as determined with the 18F-labeled fatty acid 14(R,S)-18F-fluoro-6-thia-heptadecanoic acid and with 11C-acetate in LBBB (25,26).

There is experimental evidence that early septal contraction against the relaxed LV free wall in LBBB reduces septal work load, because pressure is still low and no ejection occurs (27). On the other hand, late activation of the LV lateral wall in patients with LBBB occurs at higher stress, because the earlier activated septum has already developed tension (21,28). Our data indicate that these known alterations in ventricular mechanics result in corresponding changes in myocardial glucose metabolism, as indicated by the diminished baseline septal-to-lateral ratio of FDG uptake.

Theoretically, reduced septal work load would entail decreasing adenosine triphosphate requirements of the septum, with concomitantly diminished glucose metabolism (3). Depre et al. (29) provided indirect evidence for this hypothesis by an animal model of unloaded rat hearts being transplanted on the abdominal aorta of isogenic recipients. Gene expression for the insulin-sensitive glucose transporter GLUT-4 in these hearts decreased one day after transplantation, resulting in myocardial insulin resistance, characterized by a reduction of insulin-dependent myocardial glucose oxidation in unloaded hearts (30). This flexible regulation of cardiomyocyte gene expression could provide the pathophysiologic basis for alterations in septal glucose metabolism in the sense of septal insulin resistance in patients with HF and LBBB, which is reversed by CRT. Indeed, rapid re-expression of GLUT-4 occurred within 60 min when the energy needs increased upon reloading of rat hearts (29).

Myocardial glucose metabolism in this study was measured after an oral glucose load, which is a stimulus for insulin release. Thus, the observed reduction in septal glucose metabolism and its reversal with CRT in our study are well in accordance with the results on GLUT-4 messenger ribonucleic acid expression and insulin resistance observed in the model of unloaded and reloaded rat hearts (29,30).

Conclusions. Glucose metabolism is reduced to a greater extent than perfusion in the septum and adjacent anterior and posterior LV wall in patients with DCM and LBBB. The hemodynamic benefit of CRT is paralleled by restoration of homogeneous myocardial glucose metabolism, with less influence on perfusion.

REFERENCES

18. Saxon LA, De Marco T, Schafer J, Chatterjee K, Kumar UN, Foster E. Effects of long-term biventricular stimulation for resynchronization