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Heterogeneous Reduction of Myocardial Oxidative Metabolism in Patients With Ischemic and Dilated Cardiomyopathy Using C-11 Acetate PET

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Background The ^{11}C -acetate positron emission tomography can estimate myocardial oxidative metabolism, but previous studies have only evaluated small populations and the difference between ischemic (ICM) and idiopathic dilated cardiomyopathy (DCM) has not been fully investigated. The present aims were to evaluate global and regional myocardial oxidative metabolism in a well-characterized, large population with left ventricular (LV) dysfunction in order to clarify the metabolic differences between ICM and DCM.

Methods and Results Seventy-eight patients with ejection fraction (EF) $\leq 50\%$ (33 ICM; 45 DCM) were compared with 14 healthy controls. Myocardial oxidative metabolism was estimated with a clearance rate constant (K_{mono}) and the coefficient of variation (CV) of regional K_{mono} . Patients with LV dysfunction had reduced K_{mono} and higher CV ($p < 0.05$). In the comparison of oxidative alterations with clinical variables there was a weak correlation between K_{mono} and LVEF ($r = 0.27$). Although K_{mono} was reduced in both ICM and DCM, CV was more pronouncedly increased in ICM ($p = 0.001$). In multivariate analysis, the presence of left bundle branch block (LBBB) was an independent predictor of heterogeneous oxidative metabolism in DCM ($R^2 = 0.30$, $p < 0.0001$).

Conclusions Global reduction of myocardial oxidative metabolism occurred in both ICM and DCM. Heterogeneous oxidative metabolism was observed in these patients, especially those with ICM. Furthermore, LBBB was the independent predictor of heterogeneous oxidative metabolism in patients with DCM. (Circ J 2008; 72: 786–792)

Key Words: Carbon-11 acetate PET; Dilated cardiomyopathy; Ischemic cardiomyopathy; Left ventricular dysfunction; Myocardial oxidative metabolism

Heart failure (HF) is the final common stage of various heart diseases and has a significant effect on quality of life and prognosis. The heart relies almost exclusively on an aerobic oxidative substrate for the generation of ATP, which is required to maintain its contractile function. The balance between oxygen demand and supply is disturbed in many disease processes. The progression to HF is associated with a gradual decline in the activity of mitochondrial respiratory pathways, leading to diminished capacity for ATP production.¹ Cardiac metabolic alterations could be either adaptive or maladaptive. Furthermore, the specific etiology of HF may be of importance in the process. Cardiac metabolic alterations may correlate with the degree of left ventricular (LV) dysfunction, symptoms of HF, prognosis and the response to medical treatments.^{1–3}

For a better understanding of the pathophysiology of car-

diac metabolic alterations, it is important to measure myocardial oxygen consumption (MVO_2). The clearance kinetics of ^{11}C -acetate, measured by positron emission tomography (PET), can be used to measure tricarboxylic acid cycle flux and thus enable noninvasive quantification of myocardial oxidative metabolism at both the global and regional levels.^{2–7} The level of myocardial oxidative metabolism with failing LV systolic function has been reported to be comparable to or lower than normal LV function.^{8,9} Dyssynchrony is a predictor of poor outcome and may be associated with heterogeneity of myocardial oxidative metabolism in patients with HF. Previous studies have only evaluated rather small populations because of limited availability, and clinical significance has not been clarified in broader populations with HF. In addition, the differences between ischemic (ICM) and idiopathic dilated cardiomyopathy (DCM) have not been fully investigated.

Accordingly, the aims of this study were to evaluate myocardial oxidative metabolism by using ^{11}C -acetate PET in a cohort and to compare the oxidative alterations with clinical variables, such as symptoms of HF, left bundle branch block (LBBB) and echocardiographic parameters, in patients with ICM and DCM.

Methods

Study Population

The study population comprised 100 consecutive pa-

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tients with symptomatic HF (New York Heart Association (NYHA) class $\geq$ II) and LV systolic dysfunction (ejection fraction (EF) $\leq$ 50%) who underwent dynamic ^{11}C -acetate PET from May 2000 to December 2004. Etiology was considered ischemic in the presence of luminal stenosis $\geq$ 50% in any major epicardial coronary artery on coronary angiography, a history of myocardial infarction (MI) with electrocardiographic (ECG) evidence or prior coronary intervention procedure. The diagnosis of idiopathic DCM, based on the absence of significant luminal stenosis in any major epicardial coronary artery or primary valvular heart disease, was supported by endomyocardial biopsy. Patients were excluded if they had significant valvular heart disease ($n=8$), or hypertrophic ($n=2$) or secondary cardiomyopathy ($n=7$). Thirty-three patients with ICM (LVEF $33.1\pm 9.5\%$) and 45 with idiopathic DCM (LVEF $34.5\pm 10.9\%$) met the entry criteria.

Among 33 ICM patients, 8 (24%) had 1-vessel disease (VD), 12 had 2-VD (36%), and 13 had 3-VD (40%); 29 (88%) patients had a prior MI. There were more males in the ICM group ($p=0.03$). The prevalence of hypertension, diabetes and hyperlipidemia also tended to be higher in patients with ICM, but did not reach statistical significance. None of the ICM patients had ongoing chest pain during the PET studies. Meanwhile, a history of atrial fibrillation or ventricular arrhythmias tended to be more common in patients with DCM, but this was not significantly different ($p=0.07$ and 0.10 , respectively). There were no differences in the severity of LV dysfunction between the ICM and DCM groups in terms of LV cavity dimensions, EF, or NYHA class. The characteristics of the patients with ICM and DCM are summarized in Table 1.

The severity of HF was assessed by scoring functional class according to the NYHA class, echocardiography, and plasma B-type natriuretic peptide (BNP) measurements using a commercially available chemiluminescence enzyme immunoassay kit (MI02 SHIONOGI BNP, Shionogi Co, Ltd, Osaka, Japan) within 2 weeks of the PET studies. No clinical events or changes in medication occurred between these studies. A standard 12-lead ECG was recorded in all subjects. QRS duration was measured using the widest QRS complex from leads II, V₁ and V₆. The presence of LBBB was diagnosed on the basis of QRS duration ≥ 120 ms, absent Q wave and wide slurred R waves in V₅ and V₆, and monophasic QS or rS waves in V₁ and V₂.¹⁰

As the control group, 14 healthy volunteers (12 men, aged 30 ± 4 years) were recruited. All had a normal resting ECG, were nonsmokers and normotensive. None of them had cardiac symptoms or a history of cardiovascular disease, diabetes or hyperlipidemia. The study was approved by the Ethics Committee of Hokkaido University Hospital. Written informed consent was given by each subject.

Echocardiography

All echocardiographic examinations were performed by an experienced operator without knowledge of the clinical and PET data using a commercially available ultrasound system (3.5-MHz transducers; Sonos 5500; Hewlett-Packard, Palo Alto, CA, USA). Standard echocardiographic views of the LV were obtained, and the left atrial and ventricular dimensions and volumes were made according to standard criteria. LVEF was calculated from 2-dimensional echocardiographic images of the LV using the modified biplane Simpson's method. Left stroke volumes were measured from the LV outflow tract using pulsed Doppler measure-

Table 1 Characteristics of Patients With LV Dysfunction Secondary to ICM and DCM

	ICM ($n=33$)	DCM ($n=45$)	<i>p</i> value
Age (years)	62 ± 9	60 ± 13	0.53
Male gender	30 (91%)	31 (69%)	0.03
Hypertension	7 (21%)	4 (9%)	0.09
Diabetes mellitus	13 (39%)	8 (18%)	0.06
Hyperlipidemia	15 (45%)	10 (22%)	0.06
NYHA functional class II/III/IV	22/9/2	31/12/2	0.27
Atrial fibrillation	7 (21%)	17 (38%)	0.07
History of ventricular tachycardia/fibrillation	6 (18%)	15 (33%)	0.12
β -blockers	19 (58%)	26 (58%)	0.92
ACE inhibitors/ARB	27 (83%)	37 (83%)	1.00
BNP (ng/L)	365 ± 358	234 ± 315	0.10
LVDD (mm)	63 ± 9	61 ± 8	0.40
LVDs (mm)	53 ± 11	51 ± 9	0.65
LAD (mm)	46 ± 8	46 ± 8	0.88
LVEF (%)	33.1 ± 9.5	34.5 ± 10.9	0.55
Stroke volume (ml)	65.4 ± 17.4	60.0 ± 14.9	0.31

Data are mean $\pm$ standard deviation or number (%) of patients.

LV, left ventricular; ICM, ischemic cardiomyopathy; DCM, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BNP, N-terminal pro-brain natriuretic peptide; Dd, end-diastolic diameter; Ds, end-systolic diameter; LAD, left atrial diameter; EF, ejection fraction.

ment, and the outflow tract area was calculated assuming a circular configuration.¹¹

^{11}C -Acetate PET Scan Protocol

The ^{11}C -acetate was synthesized according to the standard method.¹² Patients were studied after at least a 5-h fast. PET was performed using a whole-body scanner (ECAT/EXACT HR+; Siemens/CTI, Knoxville, TN, USA). Each patient received normal medication including β -blockers. Transmission images were obtained using an external ring of ^{68}Ge for attenuation correction. After the 20-min transmission scan, 740 MBq of ^{11}C -acetate was administered intravenously for 60 s under resting conditions, and dynamic PET acquisition was performed (6×10 , 4×15 , 18×60 s).^{13–15} Blood pressure, heart rate and ECG were monitored during the PET scans.

^{11}C -Acetate PET Image Analysis

PET data analysis was performed using an imaging analysis package (Dr. View; Asahi-Kasei, Tokyo, Japan) and special dedicated software.^{13–16} The images were iteratively reconstructed and resliced along the short axis. Regions of interest were defined for each of these images. The reconstructed dynamic PET images were analyzed by applying a 16-segment model according to the American Society of Echocardiography, including anterior, anteroseptal, septal, inferior, posterior, and lateral walls. Each wall was subdivided into the basal and midventricular portions, and the apical anterior, septal, inferior and lateral regions.^{11,15}

Regional myocardial perfusion was based on the early myocardial uptake of ^{11}C -acetate, 60–180 s after administration.¹⁶ Segments with reduced perfusion were defined as relative tracer uptake $<50\%$ of the maximum uptake.^{15,17} To verify the relevance of oxidative metabolism in areas adjacent to the perfusion defects in patients with ICM, the segments with preserved perfusion were further subdivided into “border segments” (areas around the hypoperfusion areas) and “remote segments” (normally perfused areas remote

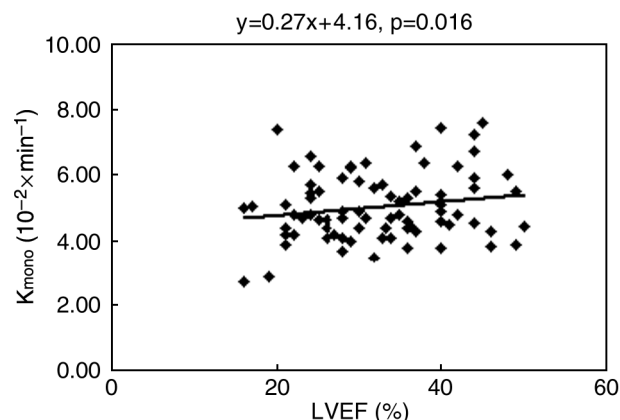


Fig 1. Correlation between left ventricular ejection fraction (LVEF) and global myocardial oxidative metabolism in patients with left ventricular dysfunction. K_{mono} , the clearance rate constant.

from the perfusion defects).

Regional oxidative metabolism was determined from the monoexponential function (K_{mono}) fit to the linear portion of the semilogarithmic plot. The start of the curve was visually defined corresponding to when the blood-pool activity had cleared (usually 3–5 min) and the curve fitting as automated^{4–6,13–15,18}. The modeling procedure resulted in 16-segment parametric polar maps of acetate clearance (rate constant, K_{mono} ; given in min^{-1}). K_{mono} values of all 16 segments of each measurement were averaged, and then the coefficient of variation (CV) of regional K_{mono} was derived as a measure of heterogeneity. To estimate the effect of perfusion defect on regional oxidative metabolism, ratios of mean K_{mono} values in segments of normal perfusion to hypoperfusion were compared on a patient basis.

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation. Comparisons between groups were assessed by Student's t-test, Mann-Whitney U-test, analysis of variance (ANOVA) or chi-square test when appropriate.

Relationship Between PET Data and Clinical Variables
By univariate analysis, we evaluated possible significant associations between the acetate PET parameter and potential covariates including age, gender, etiology of HF, NYHA class, hypertension, diabetes, hyperlipidemia, cardiac medications, ECG parameters (rhythm, QRS morphology, and history of ventricular tachyarrhythmias), heart rate and blood pressure, plasma BNP, and echocardiographic parameters (LV volumes, stroke volume, EF). Multivariate analyses were performed by stepwise multiple regression methods. The criterion for possible inclusion in the multivariable model was univariable $p < 0.10$. A p -value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata 8 software packages (StataCorp, College Station, TX, USA).

Results

Oxidative Metabolism and Cardiac Function

The hemodynamic data during PET scans were not significantly different among the ICM, DCM and control groups. Of the 78 patients with ICM or DCM, there was a weak correlation between global K_{mono} and EF ($r = 0.27$, $p = 0.016$; Fig 1). The trends were consistent in both groups but did not reach statistical difference, probably because of the small sample size (ICM: $r = 0.29$, $p = 0.10$; DCM: $r = 0.25$, $p = 0.09$). There were no correlations between K_{mono} and E/A or deceleration time on echocardiography. Overall, the patient group had a significantly reduced K_{mono} and higher CV than the control group (K_{mono} : 0.051 ± 0.010 vs $0.059 \pm 0.007 \text{ min}^{-1}$; CV: 16.7 ± 9.2 vs $9.1 \pm 2.7\%$, both $p < 0.05$). In addition, patients with either ICM or DCM had reduced

Table 2 Myocardial Oxidative Metabolism in Patients and Healthy Controls

	ICM (n=33)	DCM (n=45)	Control (n=14)	p value
SBP (mmHg)	116 $\pm$ 18	110 $\pm$ 16	116 $\pm$ 15	0.07
DBP (mmHg)	64 $\pm$ 12	60 $\pm$ 10	61 $\pm$ 13	0.08
HR (beats/min)	68 $\pm$ 13	66 $\pm$ 13	65 $\pm$ 11	0.39
RPP	7,957 $\pm$ 1,913	7,263 $\pm$ 1,888	7,458 $\pm$ 1,709	0.11
K_{mono} (min^{-1})	0.049 $\pm$ 0.009*	0.052 $\pm$ 0.011*	0.059 $\pm$ 0.007	0.03
CV (K_{mono}) (%)	21.4 $\pm$ 11.3*†	13.4 $\pm$ 5.6*	9.1 $\pm$ 2.7	0.008

Data are mean $\pm$ standard deviation.

* $p < 0.05$ vs control subjects; † $p < 0.05$ ICM vs DCM subjects.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RPP, rate-pressure product; CV, coefficient of variation. Other abbreviations see Table 1.

Table 3 Comparison of Oxidative Metabolism in Hypoperfused, Border and Remote Segments in 33 Patients With ICM (Total 496 Segments)

	Hypoperfused segments (n=195)	Non-hypoperfused segments	
		Border segments (n=111)	Remote segments (n=190)
Regional K_{mono} (min^{-1})	0.041 $\pm$ 0.009* (0.027–0.059)	0.047 $\pm$ 0.009† (0.036–0.074)	0.054 $\pm$ 0.010 (0.041–0.082)

Data are mean $\pm$ standard deviation. Values in parentheses are range.

* $p < 0.01$ hypoperfused vs other segments; † $p < 0.01$, border vs remote segments.

Abbreviation see Table 1.

Table 4 Comparisons Between DCM Patients With Normal Perfusion and Healthy Controls: Influence of LBBB

	DCM With LBBB (n=6)	DCM Without LBBB (n=33)	Controls (n=14)
<i>K_{mono}</i> (min ⁻¹)	0.049±0.013	0.052±0.011	0.059±0.007
CV (<i>K_{mono}</i>) (%)	21.1±0.6*	11.0±4.2	9.1±2.7
Septal-to-lateral <i>K_{mono}</i> ratio	0.82±0.14*	1.04±0.16	1.02±0.09

**p*<0.05 LBBB vs other groups.
LBBB, left bundle branch block. Other abbreviations see Tables 1,2.

Table 5 Determinants of CV (*K_{mono}*) (%) in Patients With DCM and Normal Perfusion (Stepwise Regression Analysis)

	β	SE	<i>p</i> value
LVDd	0.23	0.21	0.29
LVDs	0.06	1.18	0.74
LBBB	0.81	1.81	0.001

Adjusted *R*²=0.49, *p*<0.0001.
Abbreviations see Tables 1,2.

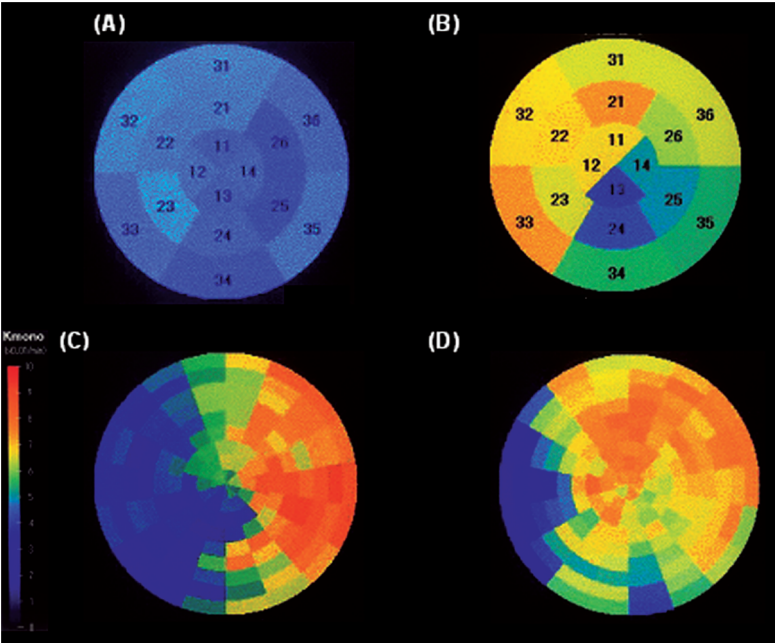


Fig 2. Polar maps of acetate the clearance rate constant (*K_{mono}*) images in (A) 57-year-old man with heart failure caused by idiopathic dilated cardiomyopathy (DCM), (B) 48-year-old woman with DCM and regional hypoperfusion in the inferolateral wall, (C) 73-year-old man with DCM and left bundle branch block (LBBB) (QRS 140ms) and (D) 63-year-old woman with DCM and Wolff-Parkinson-White (WPW) syndrome (QRS 120ms). In patient (B), concordantly reduced segmental *K_{mono}* was documented in the hypoperfused segments. Of note, in patients with LBBB (C) or WPW syndrome (D), lower *K_{mono}* was noted in the well-perfused septum.

global *K_{mono}* and increased CV with reference to the controls, especially those with ICM (*p*=0.001). Patients with ICM tended to have a lower global *K_{mono}* than those with DCM, but not reaching statistical difference (*p*=0.16). The results are shown in Table 2.

Analysis of Myocardial Oxidative Metabolism and Perfusion

Regional perfusion defects of the early uptake of acetate PET were seen in 31 of the 33 patients with ICM. Regional *K_{mono}* values in the hypoperfused, border and remote areas are shown in Table 3. The *K_{mono}* values were significantly lower in the border areas than in the remote areas (*p*<0.05, respectively).

On the other hand, a regional perfusion defect was seen in only 6 of the 45 patients with DCM. The global *K_{mono}* values were similar between patients with or without perfusion defects; segmental *K_{mono}* values were significantly lower in the hypoperfused areas (0.044±0.012 min⁻¹ range 0.030–0.079) than in the non-hypoperfused areas (0.054±0.012 min⁻¹, range 0.021–0.068; *p*=0.007). Patients with regional perfusion defects tended to have a higher CV than those without, but not reaching significance (17.6±6.6 vs 13.1±5.6%; *p*=0.08).

Heterogeneous Oxidative Metabolism in DCM and LBBB

Eight DCM patients had LBBB, and regional perfusion

defects were seen in 2 of them: 1 in the anterolateral segments and the other in the inferior segments. Of 37 DCM patients without LBBB, 4 had regional perfusion abnormalities. Therefore the remaining 39 patients with DCM showed normal perfusion: subjects with DCM and LBBB had a significantly higher CV and lower ratio of septal-to-lateral *K_{mono}* than either those without LBBB or the controls (Table 4). A larger LVDd and LVDs, and the presence of LBBB, were significantly correlated with higher CV (all *p*<0.001). By multivariate analysis, the presence of LBBB was an independent predictor of high CV in patients with DCM (Table 5). Representative images are shown in Fig 2.

Discussion

In the present study myocardial oxidative metabolism was reduced in patients with ICM and DCM. The regional heterogeneity of oxidative metabolism was greater in the patients with ICM than in those with DCM, mainly because of greater perfusion abnormalities in the former. Regional *K_{mono}* was lower in hypoperfused segments than in remote segments. Our data also show that regional heterogeneity may be used for characterizing ICM from DCM. However, we also demonstrated that regional heterogeneity exists in cases of DCM with LBBB, which might indicate different pathophysiologic processes and prognosis in the presence of LBBB.

In our study, there was a reduction in K_{mono} in areas of hypoperfusion, mainly because of reduced oxidative metabolism in the infarcted and fibrotic areas. Studies of myocardial perfusion, sympathetic function and glucose metabolism by nuclear imaging have shown that patients with ICM have more advanced perfusion and metabolic abnormalities than those with DCM.^{19–22} Patients with ischemia and scarring are expected to have regional heterogeneity in both function and metabolism. The high prevalence of a history of MI and multivessel-disease in the present study population could explain the lower and more heterogeneous oxygen metabolism.^{8,15,17,23} We also found that oxidative metabolism was lower in the border segments than in remote ones with regard to hypoperfused areas.^{18,24} Hypoperfused segments could represent the core of the infarct and the neighboring segments could be partially infarcted. They might also reflect accelerated myocardial metabolism in remote regions in the process of LV remodeling.

The heart is unique among organ systems in its metabolic regulation, and the relationship between contractile function and oxidative metabolism could be complex. Our results suggest that acetate PET is a potential imaging modality for identifying clinical phenotypes and underlying pathophysiologic mechanisms.²⁵ We quantitatively estimated the heterogeneity of oxidative metabolism using CV values, an index that may be helpful in serial evaluation, especially for treatment response. Our data show that regional inhomogeneity exists in non-ischemic DCM with LBBB, as previously reported.^{26,27} In the present study, regional hypoperfusion was not uncommon in DCM patients, and reduced oxygen metabolism was frequently observed in these areas. Besides focal myocardial fibrosis,^{22,27–29} recent studies have suggested that perfusion and metabolism may be affected by endothelial dysfunction in DCM.^{30–32} LBBB is known to impair LV mechanical function and is an important predictor of cardiac mortality in patients with HF caused by DCM.^{10,33} Previous studies found that perfusion and glucose metabolism were reduced in cases with LBBB,^{34–42} and the extent of scarring correlates with QRS duration.²⁹ Our data show reduced septal K_{mono} values in the comparison of the lateral walls in patients with DCM and LBBB, and the presence of LBBB appeared to be independent of the heterogeneous metabolic changes. This result implies that LBBB may not always be caused by direct involvement of the conducting system, but rather by widespread myocardial fibrosis. We did not find significant oxidative differences in cases of right bundle branch block (RBBB), indicating different electrical activation abnormalities between LBBB and RBBB.⁴³ However, we did not quantify right ventricular oxidative metabolism, so our approach may not accurately reflect the metabolic alterations in patients with RBBB.⁹

Previous reports have suggested that cardiac resynchronization therapy (CRT) can ameliorate the perfusion and metabolism alterations, as well as reversing LV remodeling, and may be beneficial to myocardial efficiency;^{44–49} however, 20–30% of patients still do not respond.^{50,51} Acetate PET could provide additional biologic information about the myocardium at both regional and global levels, which might guide decision making and monitor the therapeutic response. Recent studies have suggested that delayed enhancement (DE) on contrast-enhanced MRI represents irreversible myocardial injury.^{52,53} There is limited information about the correlation between the presence of DE on MRI and acetate PET findings. Combined assessment of oxygen

metabolism and tissue composition might be incrementally beneficial for predicting functional improvement after CRT.

Study Limitations

First, aging has an impact on substrate metabolism in heart, and the controls in the present study were much younger. However, overall $\dot{M}V\text{O}_2$ was higher in the older subject, so the age factor would not affect the conclusions of our results.⁵⁴ CV was also significantly lower in the controls and the influence of aging on CV is unknown. The difference in global K_{mono} between the control and HF groups might be partly explained by the effect of β -blockers. Second, we assessed resting perfusion from the initial uptake of ^{11}C -acetate and did not evaluate possible interference of inducible ischemia according to the extent of scarring. The border areas (>50% of the maximum uptake) could include non-transmural infarcted or stress-induced ischemic myocardium, which might affect the correct estimation of altered oxidative metabolism and perfusion in the border and remote segments. Thus compensatively increased oxidative metabolism in the remote areas compared with border areas should be interpreted cautiously. There was a higher prevalence of atrial fibrillation and ventricular arrhythmias among DCM patients in this series, which could be the result of a selection bias in a tertiary referral center. Third, validation data were not available. However, several studies have shown the usefulness and accuracy of K_{mono} assessed by ^{11}C -acetate PET. Fourth, the present data do not address the prognostic value of acetate PET imaging, because of the limited number of patients with severe HF in our study population. A future study with a large sample of patients that have severe LV dysfunction is warranted.

In conclusion, the present patients with HF had reduced and heterogeneous myocardial oxidative metabolism, especially those with ICM. In patients with DCM, the oxidative inhomogeneity was associated with the presence of LBBB. These findings contribute to a better understanding of the pathophysiology of LV dysfunction in relation to global oxidative metabolism and oxidative metabolic heterogeneity in patients with cardiomyopathy.

Disclosure

The authors indicate that they have no financial conflicts of interest.

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