Original Article

Effects of Cardiac Energy Efficiency in Diastolic Heart Failure: Assessment with Positron Emission Tomography with ^{11}C-Acetate

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Diastolic heart failure (DHF) has become a high social burden, and its major underlying cardiovascular disease is hypertensive heart disease. However, the pathogenesis of DHF remains to be clarified. This study aimed to assess the effects of cardiac energy efficiency in DHF patients. ^{11}C-Acetate positron emission tomography and echocardiography were conducted in 11 DHF Japanese patients and 10 normal volunteers. The myocardial clearance rate of radiolabeled ^{11}C-acetate was measured to calculate the work metabolic index (WMI), an index of cardiac efficiency. The ratio of peak mitral E wave velocity to peak early diastolic septal myocardial velocity (*E*/*e*′) was calculated to assess left ventricular (LV) filling pressure. The LV mass index was greater and the mean age was higher in the DHF patients than in the normal volunteers. There was no difference in WMI between the two groups. However, WMI varied widely among the DHF patients and was inversely correlated with *E*/*e*′ (r=−0.699, p=0.017). In contrast, there was no correlation in the normal volunteers. In conclusion, the inefficiency of energy utilization is not a primary cause of diastolic dysfunction or DHF, and cardiac efficiency may not affect diastolic function in normal hearts. However, the energy-wasting state may induce the elevation of LV filling pressure in DHF patients, which was considered to principally result from the progressive diastolic dysfunction. (*Hypertens Res* 2008; 31: 1157–1162)

***Key Words*: diastole, heart failure, metabolism, positron emission tomography**

Introduction

Clinical studies have revealed that 40% to 50% of patients with heart failure have normal or minimally depressed left ventricular (LV) ejection fraction (EF) (*1–4*). This type of heart failure is principally caused by diastolic dysfunction (*5*, *6*) and is termed diastolic heart failure (DHF). Our experimental studies have shown that the progression of diastolic dysfunction in DHF model rats is accompanied by LV hypertrophy, fibrosis and alteration of the Ca handling protein (*7–11*). Recently, Borbély *et al*. showed that myocyte stiffness is enhanced in DHF patients and is reversed by the administration of protein kinase A (*12*). Their results suggest that the abnormality in myocardial metabolism for energy production and the subsequent impairment of cardiac efficiency are closely related to the development of DHF.

Acetate is extracted by myocytes, and 80% to 90% of acetate undergoes oxidation *via* the tricarboxylic acid cycle (*13*). The principal metabolite of acetate, CO_2, is cleared rapidly from the myocytes. Therefore, myocardial clearance of acetate directly reflects tricarboxylic acid cycle flux and oxida-

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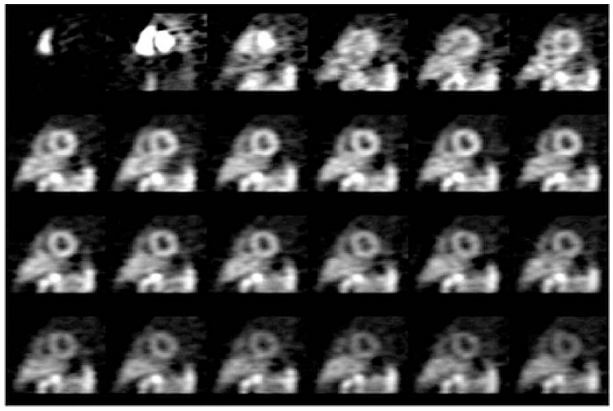

Fig. 1. *Short axis images of ^{11}C-acetate PET at the mid-ventricular level in 24 frames for 20 min.*

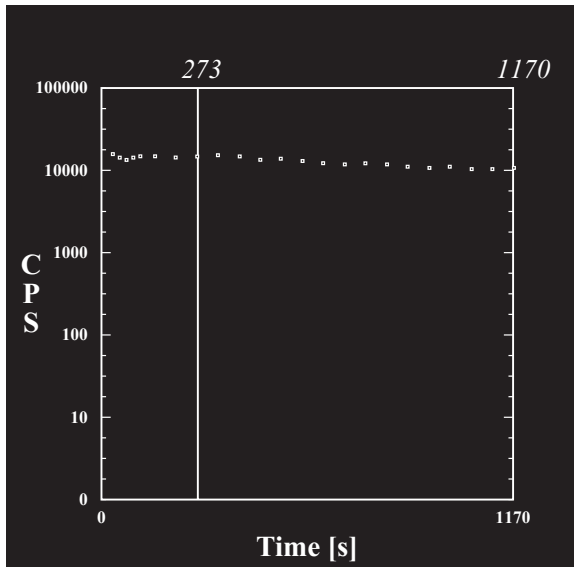

Fig. 2. *Time-activity curve of ^{11}C-acetate in the regions of interest set on the left ventricular wall. The counts per second are shown with a logarithm in the ordinate. A monoexponential function was fit to this myocardial time-activity data, and the clearance rate constant k (k_{mono}) was determined. CPS, counts per second.*

tive metabolism. The myocardial clearance rate of radiolabeled ^{11}C-acetate can be noninvasively determined using positron emission tomography (PET), and has been used to measure rates of oxidative metabolism and myocardial oxygen consumption (*14*), which also enables the calculation of cardiac efficiency. In patients with heart failure and systolic dysfunction, the impairment of cardiac energy efficiency was closely related to the reduction of EF (*15*, *16*). However, its effects remain unclear in DHF patients with preserved EF.

This clinical study aimed to investigate the effects of abnormality of myocardial metabolism on the energy production in the development of DHF.

Methods

Patients

Eleven Japanese patients with DHF in our outpatient clinics and 10 normal volunteers participated in this study. All of the DHF patients met the modified Framingham criteria of heart failure (*1*, *17*), and the LVEF of all the study subjects was ≥50%. Patients with congenital heart disease, severe valve disease, chronic obstructive lung disease or restrictive lung disease were not included in the DHF group. This study complies with the Declaration of Helsinki. The Osaka University Hospital Ethics Committee approved the study protocol, and written informed consent was obtained from all of the patients.

Study Protocol

The study subjects were referred for ^{11}C-acetate PET, echocardiography and measurement of right and left bilateral brachial-ankle pulse wave velocities (PWVs). For ethical reasons, medications were not withheld from the DHF patients at the start of this study. Angiotensin converting enzyme inhibitors were prescribed to 7 patients, angiotensin receptor blockers to 4 patients, β-blockers to 8 patients, calcium channel blockers to 10 patients, and diuretics to 8 patients.

^{11}C-Acetate PET Imaging

The study subjects were positioned in a whole-body PET scanner (Headtome 5; Shimadzu, Kyoto, Japan) at Osaka University Hospital. A 10-min transmission scan was performed to correct the emission images for photon attenuation. Immediately after the transmission scan, about 600 MBq of ^{11}C-acetate was administered intravenously for 30 s, and a dynamic PET acquisition was initiated simultaneously (20 s × 6 + 60 s × 18 = 24 frames). During the emission scan, the blood pressure and heart rates were measured.

Regions of interest (n=8; size 5×5 pixels) were defined over the LV myocardium of the anterior, lateral, inferior, septal wall on the basal and mid-ventricular short axial image planes (Fig. 1). These regions were then applied to the corresponding images in the dynamic sequence, yielding myocardial time-activity curves. A monoexponential function was fit to the myocardial time-activity data, and the clearance rate constant k (k_{mono}) was determined as described previously (Fig. 2) (*14*). Because the monoexponential fit began at the point when the blood pool was stable (5 min after injection), the spillover from the blood pool to the myocardium was not corrected. The mean value of k_{mono} in the 8 regions was used in the following analysis.

Table 1. The Characteristics of the Normal Volunteers and the DHF Patients

	Normal volunteers	DHF
n	10	11
Sex (female/male)	0/10	6/5
Age (years old)	36±8	72±11*
Systolic blood pressure (mmHg)	116±9	123±16
Diastolic blood pressure (mmHg)	77±11	66±13*
Heart rate (/min)	65±7	62±13
LVEF (%)	66±6	65±10
LV end-diastolic dimension (mm)	49±4	49±7
LV end-systolic dimension (mm)	31±4	32±7
Stroke volume index (mL/min/m^2)	41±8	42±11
Isovolumetric relaxation time (ms)	78±17	102±22*
Deceleration time of the mitral E wave velocity (ms)	181±22	223±50*
E/*A*	1.6±0.3	1.2±0.9
E/*e*′	7.4±1.5	14.5±6.0*
LV mass index (g/m^2)	79±22	130±42*
PWV (cm/s)	1,270±86	1,697±268*
k_{mono} (/min)	0.053±0.011	0.055±0.014
WMI ($\times 10^5$ mmHg mL/m^2)	58.9±12.8	60.1±17.8

Values are expressed as mean±SD. *$p<0.05$ *vs*. normal volunteers. DHF, diastolic heart failure; LVEF, left ventricular ejection fraction; LV, left ventricular; *E*, peak mitral E wave velocity; *A*, peak mitral A wave velocity; *e*′, peak early diastolic velocity of the septal mitral annulus; PWV, pulse wave velocity; k_{mono}, clearance rate constant; WMI, work metabolic index.

Echocardiography

Doppler echocardiography was performed with a commercially available echocardiograph (Aplio; Toshiba, Tokyo, Japan) as previously described (*18–20*). As all of the study subjects were in sinus rhythm, the pulsed Doppler transmitral flow velocity curve was recorded to measure the peak mitral E wave velocity (*E*), the peak mitral A wave velocity (*A*), the deceleration time of the mitral E wave velocity and the isovolumetric relaxation time. LVEF was assessed by Simpson's method. Stroke volume was calculated as a product of the LV outflow area and the time-velocity integral of the LV outflow velocity curve, and the stroke volume index was defined as the ratio of the stroke volume to the body surface area. LV mass was calculated with the formula derived from the data of the American Society of Echocardiography (*21*), and LV mass index was defined as the ratio of LV mass to body surface area. Doppler tissue imaging of the septal mitral annulus was obtained from the apical 4-chamber view to measure peak early diastolic velocity (*e*′) to calculate the ratio of *E* to *e*′ (*E*/*e*′) as a parameter of left atrial pressure and LV diastolic function (*22–24*).

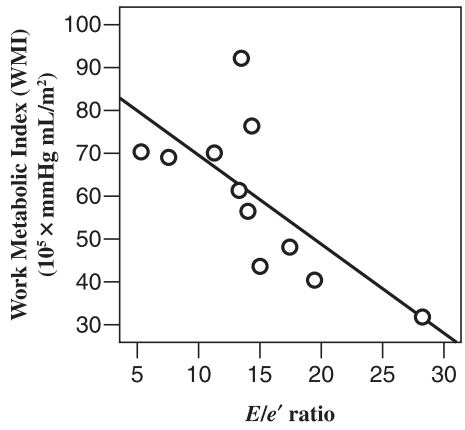

Fig. 3. *Relationship between the work metabolic index (WMI) and E/e′ ratio. There was a significant correlation ($r=-0.699$, $p=0.017$).*

Calculation of Cardiac Efficiency

The work metabolic index (WMI), an index of cardiac efficiency, was calculated as follows:

$$\text{WMI } (10^5 \times \text{mmHg mL/m}^2) = (\text{systolic blood pressure} \times \text{heart rate} \times \text{stroke volume index})/k_{mono}.$$

The product of blood pressure, heart rate and stroke volume was used as an index of the cardiac external work. The k_{mono} measured by ^{11}C-acetate PET was used as an index of myocardial oxygen consumption (*15*).

PWVs

PWVs were measured with a Form® PWV/ABI device (Nippon Colin, Komaki, Japan) to evaluate the elasticity of the arterial wall (*25*). The averaged value of the right- and left-PWVs was used in the following analysis.

Statistical Analysis

Individual parameter values were averaged and expressed as the mean values±SD. Simple linear regression analysis with Pearson's correlation coefficient was used to describe correlation between continuous variables. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 11 DHF patients, 10 had hypertension, 7 had diabetes mellitus, and 4 had a history of coronary artery disease. Coronary revascularization had been conducted in all 4 of the patients with a history of coronary artery disease, and none

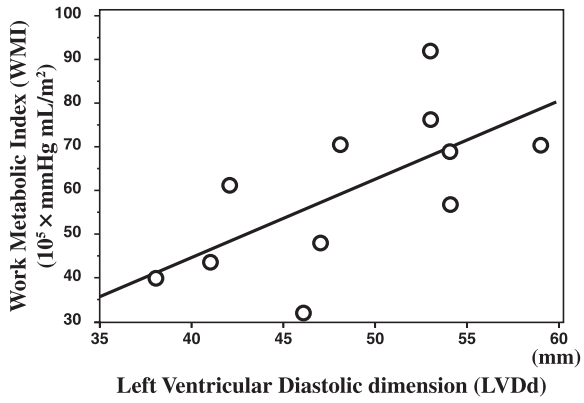

Fig. 4. *Relationship between the work metabolic index (WMI) and left ventricular end-diastolic dimension (LVDd). There was a significant correlation (r = 0.653, p = 0.029).*

showed symptoms of angina. As shown in Table 1, the mean age was higher and diastolic blood pressure was lower in the DHF patients than in the normal volunteers. The LV mass index and PWV were increased in the DHF patients. Eight DHF patients showed LV hypertrophy according to the criteria of the American Society of Echocardiography (*26*), and the age of the other 3 DHF patients without LV hypertrophy was more than 70 years old. The isovolumetric relaxation time, the deceleration time of the mitral E wave velocity, and the E/e' were greater in the DHF patients than in the normal volunteers, which is compatible with the impairment of diastolic function in the DHF patients. There was no significant difference in k_{mono}, an index of myocardial oxygen consumption, and WMI, an index of cardiac efficiency, between the two groups.

Relation between WMI and Echocardiographic Indices

There was no significant difference in WMI between the two groups (Table 1), indicating that the inefficiency of energy utilization is not a primary cause of diastolic dysfunction or DHF. However, the WMI and E/e' ratio, an index of left atrial pressure (*22*), varied widely and showed an inverse correlation ($r=-0.699$, $p=0.017$; Fig. 3) in the DHF patients. WMI tended to show a positive correlation with e', an index of LV relaxation (*27*) ($r=0.544$, $p=0.083$). In addition, WMI was positively correlated with LV end-diastolic diameter ($r=0.653$, $p=0.029$; Fig. 4). There was no significant correlation between WMI and any other echocardiographic indices in the DHF patients (Table 2). WMI did not correlate with PWV ($r=0.194$, $p=0.568$). In the normal volunteers, WMI did not correlate with any echo-Doppler indices (Table 2).

Table 2. Correlation Coefficient between WMI and Echocardiographic Indices in Each Group

	Normal volunteers	DHF
LVEF	0.501	−0.485
LV end-diastolic dimension	0.277	0.653*
Isovolumetric relaxation time	0.303	−0.068
Deceleration time of the mitral E wave velocity	0.114	−0.132
E	0.305	−0.371
E/*A*	0.194	−0.155
E/e'	−0.189	−0.699*
e'	0.528	0.544
LV mass index	0.337	0.253

*$p<0.05$. WMI, work metabolic index; DHF, diastolic heart failure; LVEF, left ventricular ejection fraction; LV, left ventircular; *E*, peak mitral E wave velocity; *A*, peak mitral A wave velocity; e', peak early diastolic velocity of the septal mitral annulus.

Discussion

WMI, which was noninvasively estimated with ^{11}C-acetate PET and echocardiography, was not different between the DHF patients and the normal volunteers. However, WMI varied widely among the DHF patients and was inversely correlated with the E/e' ratio, an index of left atrial pressure and LV diastolic function (*22–24*). There was no correlation in the normal volunteers.

Bengel *et al*. showed that cardiac energy efficiency was impaired in heart failure patients with systolic dysfunction, and that the energy waste was closely related to the reduction of EF (*16*). The present study is the first to show that DHF is not necessarily characterized by the cardiac energy waste—in contrast to heart failure with systolic dysfunction, which is characterized by such waste—and this may be partly attributable to the finding that EF was not reduced in the DHF patients.

However, the current study suggests that the energy waste contributed to the development of DHF. The inverse correlation between WMI and the E/e' ratio in the DHF patients indicates that energy waste was associated with an increase in LV filling pressure due to progressive diastolic dysfunction. The mean value of the LV mass index was increased, and the mean age was much higher in the DHF patients compared to the normal volunteers. Although the cardiac energy waste is unlikely to primarily induce diastolic dysfunction or DHF in normal hearts, the impairment of cardiac efficiency may promote diastolic dysfunction and induce DHF in the hypertrophied and/or aged heart.

Kawaguchi *et al*. previously suggested that the cardiac energy cost of increasing stroke volume was elevated in DHF patients, based on data on the pressure-volume relation (*28*), which is not consistent with our conclusion that DHF is not necessarily characterized by the cardiac energy waste. This discrepancy may be explained as follows. First, the greater elevation of left atrial pressure that was considered to principally result from the progressive diastolic dysfunction was

associated with less energy efficiency in this study. Thus, the severity of diastolic dysfunction of the study subjects may have differed between the previous and current studies. Second, we directly estimated tricarboxylic acid cycle flux and oxidative metabolism using PET, but the previous study indirectly assessed energy cost using model-based prediction with the pressure-volume relation.

Borbély *et al*. showed myocyte stiffening in DHF patients and its reversal by the administration of protein kinase A (*12*), and van Heerebeek *et al*. showed that myocardial stiffness was higher in DHF patients than in patients with systolic heart failure (heart failure with low EF) (*29*). Their results suggest that abnormality in the cAMP-protein kinase A–related pathway plays important roles in the development of diastolic dysfunction and DHF, and support our conclusion that the energy waste is likely to promote the elevation of LV filling pressure in DHF patients, which is considered to principally result from the progressive diastolic dysfunction. However, the fundamental mechanisms of the impairment of energy efficiency in DHF remain unclear. The lack of correlation between WMI and the LV mass index or PWV suggests that LV hypertrophy or afterload elevation is not a principal cause of the impairment of cardiac efficiency in the DHF patients, and further studies will be needed to examine this issue.

There was not a statistically significant correlation between WMI and e', an index of LV relaxation (*27*), in this study; however, this does not necessarily deny a relation between WMI and LV diastolic function. LV diastolic function consists of several factors, and LV relaxation is only one of them. Another important factor is ventricular/myocyte stiffness, and our previous experimental study demonstrated that the abnormality of myocardial stiffness rather than LV relaxation is mainly responsible for the elevation of LV filling pressure and the transition from LV diastolic dysfunction to DHF (*5*). WMI may be more related to myocardial stiffness than to LV relaxation.

This study showed that a decrease in LV end-diastolic dimension was associated with the deterioration of WMI in the DHF patients (Fig. 4). A small LV cavity size is one of the characteristics of DHF (*6*, *24*), and may lead to the lack of LV dilatation and the excessive increase in LV filling pressure during exercise in DHF patients (*30*). Thus, the association of a small LV cavity size with poor energy efficacy may reflect the close relation between energy waste and both poor diastolic functional reserve and severe LV diastolic dysfunction in DHF patients.

Study Limitations

First, the number of study subjects was small, and the effects of patient characteristics such as age, medications, or causes of DHF on cardiac energy efficiency remain to be clarified in future studies. Second, the severity of diastolic dysfunction was assessed by echocardiography, not by cardiac catheterization. However, it is ethically difficult to conduct cardiac catheterization only to assess LV filling pressure and diastolic function. In addition, the E/e' ratio is recognized as an established index to assess LV filling pressure and the severity of diastolic dysfunction in the chronic stable stage (*24*) and is now widely used even in clinical trials (*31–33*).

Conclusions

The inefficiency of energy utilization does not primarily cause diastolic dysfunction or DHF in normal hearts, but may induce an elevation of LV filling pressure, which is considered to principally result from progressive diastolic dysfunction, and thereby lead to DHF in hypertrophied and/or aged hearts. Currently, there is no established therapeutic strategy for DHF. The prognosis of DHF has not changed in the past two decades, in contrast to the significant improvement of prognosis in patients with systolic heart failure (*34*). Our results suggest that improvement of cardiac efficiency may be a target for the treatment of DHF.

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