

ORIGINAL ARTICLE

Left ventricular global systolic dysfunction has a significant role in the development of diastolic heart failure in patients with systemic hypertension

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Regional left ventricular (LV) systolic dysfunction has been identified in diastolic heart failure (DHF). However, the relationship between regional or global LV systolic function and heart failure symptoms in DHF has not been evaluated in detail. The present study evaluates such relationships in patients with systemic hypertension (HT) and DHF. We assessed LV systolic and diastolic function in 220 consecutive patients with systemic HT and in 30 normal individuals (Control) using Doppler echocardiography. Patients with HT were assigned to groups with DHF, asymptomatic diastolic dysfunction (ADD) and no diastolic dysfunction (Simple HT). Ejection fraction in DHF was significantly decreased ($63 \pm 8\%$) compared with the Control, Simple HT and ADD groups (67 ± 5 , 66 ± 7 and $68 \pm 8\%$, respectively). Isovolumetric contraction time in DHF (70 ± 30 msec) was significantly increased compared with those in the ADD, Simple HT and Control groups (31 ± 17 , 31 ± 15 and 30 ± 19 msec, respectively). Mitral annular systolic velocities were significantly decreased in the DHF and ADD groups (6.4 ± 1.5 and 7.2 ± 1.3 cm sec⁻¹, respectively) compared with those in the Simple HT and Control groups (8.5 ± 1.8 and 8.4 ± 3.0 cm sec⁻¹, respectively), and in the DHF group compared with the ADD group. LV global systolic dysfunction has a significant role in the development of heart failure symptoms associated with DHF in patients with systemic HT.

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INTRODUCTION

Whether left ventricular (LV) systolic properties are reduced in diastolic heart failure (DHF) remains controversial, because patients with DHF maintain a normal stroke volume and ejection fraction (EF) at rest. Some evidence suggests that LV systolic function is normal in DHF and that LV diastolic dysfunction is the main abnormality,^{1–3} whereas other evidence suggests that the systolic function of the LV is abnormal in DHF, as well as the diastolic function.^{4–10} Systolic function comprises regional and global systolic function. We described the importance of cardiac time interval analysis to evaluate the global systolic function in patients with DHF consisting of ischemic heart disease, hypertrophic cardiomyopathy or hypertensive heart diseases, and showed that DHF is associated with global systolic dysfunction.¹¹ However, the relationship between heart failure symptoms and regional or global LV systolic dysfunction in DHF has not been fully evaluated. Because DHF comprises several diseases, the systolic function may become heterogeneous if we analyze the function in DHF patients with several diseases. To accurately assess the relationship between heart failure symptoms and the regional or global LV systolic

dysfunction in DHF, it would be better to determine the function in a single heart disease with DHF.

Systemic hypertension (HT) remains the most common, readily identifiable and reversible risk factor for cardiovascular diseases. Both structural and functional myocardial abnormalities identified in hypertensive patients contribute to the progression of myocardial dysfunction from asymptomatic status to clinically apparent heart failure. We postulated that global systolic dysfunction has a significant role in the development of heart failure symptoms in hypertensive patients with DHF. We therefore evaluated the relationships between global and regional systolic and diastolic function and heart failure symptoms in patients with systemic HT using Doppler echocardiography.

METHODS

Study participants

The Ethics Committee of Kagoshima University Hospital approved the study protocol and 223 consecutive patients with systemic HT and 30 age-matched healthy individuals (Control) provided written informed consent to participate.

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Of the patients with HT, 50 had DHF, 39 had asymptomatic diastolic dysfunction (ADD), and 131 were asymptomatic and without diastolic dysfunction (Simple HT). We diagnosed DHF using the criteria of the European Society of Cardiology established in 2007,¹² including signs or symptoms of heart failure, LVEF >50%, LV end-diastolic volume index of <97 ml m⁻² and evidence of diastolic dysfunction according to tissue Doppler echocardiography and/or B-type natriuretic peptide level ($E/E' > 15$ or $8 > E/E' \geq 15$, where E and E' are the early diastolic mitral flow velocity and early diastolic mitral annulus velocity, respectively, and B-type natriuretic peptide > 200 pg dl⁻¹). Three patients were excluded because of EF < 50% or LV end-diastolic volume index > 97 ml m⁻². We defined ADD as no signs, symptoms or history of congestive heart failure, but with echocardiographic criteria indicating diastolic dysfunction and a preserved LVEF. Simple HT was defined as other HT without ADD or DHF. Physical, chest X-ray, electrocardiographic and echocardiographic findings were normal in the Controls, none of them had a history of cardiovascular disease. Patients with atrial fibrillation, first-degree atrioventricular block, moderate/severe mitral or aortic valve diseases, or other cardiovascular diseases, were excluded from the study. Patients who received treatment for renal or hepatic disease were also excluded.

Echocardiography

All participants were examined by two-dimensional (2D) and Doppler echocardiography using 1–5 MHz phased array transducers and standard equipment (Vivid 7, GE Healthcare, Milwaukee, WI, USA). Filters were set to the minimum so that eliminating low velocities would not result in erroneous data. All Doppler and echocardiographic measurements proceeded according to the recommendations of the American Society of Echocardiography.^{13,14} The end-diastolic and end-systolic LV volumes, LV stroke volumes, and EF were obtained using the modified biplane Simpson's method. Left atrial volumes were calculated using the biplane area-length method. Relative wall thickness and LV mass were calculated using standard linear dimensions.

Mitral flow velocity was recorded in the apical four-chamber view by placing the sample volume of the pulsed wave Doppler echocardiography at the mitral valve tip. The LV outflow velocity was recorded in the apical long-axis view by placing the sample volume at the LV outflow tract. E and late diastolic mitral flow velocity were also measured. Tissue Doppler images of the medial and lateral mitral annulus were obtained from the apical four-chamber view. E' and late diastolic velocity and systolic velocity (S') of the mitral annulus were measured. These variables were individually analyzed as the average of the medial and lateral sites, and E/E' was calculated. Doppler time intervals were measured from the mitral inflow and the LV outflow velocities (Figure 1). Interval a was measured from the cessation of the mitral inflow to the onset of the next inflow. Interval b (ejection time) was measured from the onset of the LV outflow velocity to its cessation. The LV Tei index, defined as the sum of the isovolumetric contraction and relaxation times divided by the ejection time (ET), was calculated as $(a-b)/b$.¹⁵ The LV isovolumetric relaxation time was obtained by subtracting interval d , between the R wave on the electrocardiogram and the cessation of LV ejection flow, from interval c , between the R wave and the onset of mitral inflow. We then obtained the LV isovolumetric contraction time (ICT) by subtracting the isovolumetric relaxation time from $(a-b)$. The ratio of ICT divided by ET (ICT/ET) was also calculated (Figure 1).^{15–18} Right ventricular pressure was calculated as tricuspid regurgitation (TR) velocity from continuous wave Doppler echocardiography and obtained from the following equation: Right ventricular pressure = $4(\text{TR velocity})^2 + 10$ (mm Hg). All measurements were obtained from three consecutive beats and averaged.

Reproducibility

Inter- and intra-observer variability was determined as the difference between repeated LV ICT measurements in 20 patients by two independent observers and by the same observer, respectively.

Statistical analysis

The continuous variables are expressed as means \pm s.d. The significance of differences among groups was tested using the one-way analysis of variance, with subgroup analysis by the Scheffé test. Categorical variables are expressed as

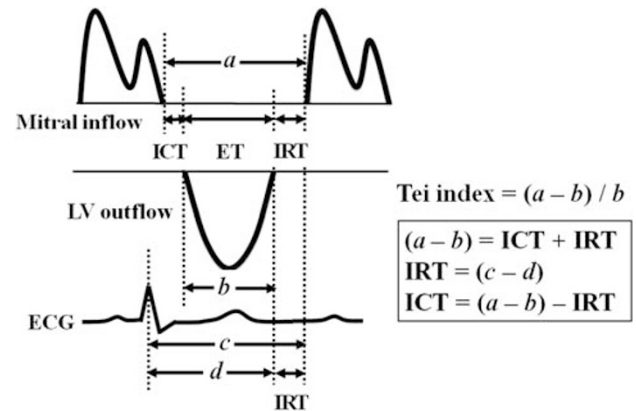


Figure 1 Schema of mitral flow and left ventricular (LV) outflow velocities used to measure Doppler cardiac time intervals. a , Interval between cessation and onset of mitral inflow, which is the sum of LV isovolumetric contraction time (ICT), LV ejection time (ET) and isovolumetric relaxation time (IRT); b , LV ET; c , interval between R wave on electrocardiogram (ECG) and onset of mitral inflow; d , interval between R wave on ECG and cessation of LV outflow.

the frequency (percentage), and were compared using the χ^2 test. A P -value of <0.05 was considered significant.

RESULTS

Participants

Table 1 shows the characteristics of the study groups. Age, gender distribution, body surface area and heart rate did not significantly differ among the four groups.

All patients in the Simple HT and ADD groups were New York Heart Association (NYHA) class I. Those in the DHF group comprised class I, $n=0$; class II, $n=36$; class III, $n=14$ and class IV, $n=0$. Heart rates did not significantly differ among the four groups. Systolic and diastolic blood pressure was significantly higher in the Simple HT, ADD and DHF groups compared with the Control group. Systolic and diastolic blood pressure did not significantly differ among the Simple HT, ADD and DHF groups.

Global LV systolic function

The EF in all groups was >60%, but that in the DHF group was significantly decreased compared with the Control, Simple HT and ADD groups. Stroke volume in the DHF group was significantly increased compared with that in the Simple HT group (Table 2). Both ICT and ICT/ET were significantly increased in the DHF group compared with the Control, Simple HT and ADD groups (Figure 2). Neither ICT nor ICT/ET significantly differed among the Control, Simple HT and ADD groups (Table 3).

Regional LV systolic function

The S' value was significantly decreased in the ADD and DHF groups compared with those in the Control and Simple HT groups, and in the DHF group compared with the ADD group (Table 2, Figure 3).

LV diastolic function

The E velocities in the ADD and DHF groups were significantly higher than those in the Control and Simple HT groups. The E' velocities in the Simple HT, ADD and DHF groups were significantly decreased compared with those in the Control group, and those in the ADD and DHF groups were significantly decreased compared with those in the

Table 1 Patients' characteristics

	Control (n=30)	Simple HT (n=131)	ADD (n=39)	DHF (n=50)	P-value by χ^2 -test or ANOVA
Age (years)	63 ± 13	65 ± 10	67 ± 12	65 ± 12	NS
Male/Female	15/15	72/59	19/20	29/21	NS
BSA (m ²)	1.63 ± 0.18	1.62 ± 0.18	1.62 ± 0.21	1.64 ± 0.20	NS
NYHA class I/II/III/IV	–	131/0/0/0	39/0/0/0	0/36/14/0	
Hypertension	0	131	39	50	P<0.0001
Diabetes mellitus	0	19 (15%)	13 (33%)	20 (40%)	P<0.001
<i>Hemodynamics</i>					
Heart rate (b.p.m.)	72 ± 13	70 ± 12	68 ± 14	67 ± 12	NS
Systolic BP (mm Hg)	122 ± 10	136 ± 17*	140 ± 22*	139 ± 17*	P<0.0001
Diastolic BP (mm Hg)	67 ± 6	79 ± 10*	79 ± 10*	78 ± 12*	P<0.0001
<i>Medications (%)</i>					
β-blockers	0	16 (12%)	9 (23%)	16 (32%)	P<0.001
ACEI or ARB	0	82 (63%)	27 (69%)	27 (54%)	P<0.0001
Diuretics	0	12 (9%)	5 (13%)	20 (40%)	P<0.0001
Calcium antagonists	0	85 (65%)	23 (59%)	22 (44%)	P<0.0001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADD, asymptomatic diastolic dysfunction; ANOVA, analysis of variance; ARB, angiotensin receptor blocker; BSA, body surface area; DHF, diastolic heart failure; HT, hypertension; NS, not significant; NYHA, New York Heart Association.

*P<0.0001 relative to Control.

Table 2 Echocardiographic data

	Control (n=30)	Simple HT (n=131)	ADD (n=39)	DHF (n=50)	P-value by ANOVA
LVEDVI (ml m ⁻²)	43 ± 8	42 ± 12	44 ± 15	52 ± 14 ^{*,†,‡}	P<0.0001
LVESVI (ml m ⁻²)	14 ± 4	14 ± 6	14 ± 6	20 ± 8 ^{*,†,‡}	P<0.0001
EF (%)	67 ± 5	66 ± 7	68 ± 8	63 ± 8 ^{*,†,‡}	P<0.01
Stroke volume (ml)	48 ± 11	45 ± 14	49 ± 18	53 ± 14 [†]	P<0.0001
LAVI (ml m ⁻²)	22 ± 8	25 ± 12	30 ± 13 ^{*,†}	36 ± 16 ^{*,†,‡}	P<0.0001
Septal wall thickness (mm)	10 ± 1	11 ± 2	14 ± 2 ^{*,†}	14 ± 2 ^{*,†}	P<0.0001
PW thickness (mm)	10 ± 1	11 ± 1	13 ± 1 ^{*,†}	12 ± 2 ^{*,†}	P<0.0001
LV mass index (g m ⁻²)	89 ± 22	100 ± 25*	138 ± 26 ^{*,†}	140 ± 36 ^{*,†}	P<0.0001
Relative wall thickness	0.48 ± 0.07	0.49 ± 0.08	0.56 ± 0.07 ^{*,†}	0.53 ± 0.11 ^{*,†}	P<0.0001
<i>Mitral Doppler flow</i>					
E (cm s ⁻¹)	59 ± 13	60 ± 15	71 ± 18 ^{*,†}	72 ± 21 ^{*,†}	P<0.0001
A (cm s ⁻¹)	72 ± 20	76 ± 18	80 ± 20	78 ± 22	NS
DT (ms)	215 ± 49	215 ± 49	217 ± 49	222 ± 58	NS
<i>Tissue Doppler imaging</i>					
E' (cm s ⁻¹)	8.7 ± 2.5	7.6 ± 1.9*	5.4 ± 1.6 ^{*,†}	5.2 ± 1.7 ^{*,†}	P<0.0001
E/E'	7.1 ± 2.4	8.2 ± 2.1*	13.7 ± 3.5 ^{*,†}	14.6 ± 5.4 ^{*,†}	P<0.0001
S' (cm s ⁻¹)	8.4 ± 3.0	8.5 ± 1.8	7.2 ± 1.3 ^{*,†}	6.5 ± 1.5 ^{*,†,‡}	P<0.0001
RV pressure (mm Hg)	29.2 ± 4.3	31.0 ± 4.9	33.1 ± 5.7*	33.9 ± 7.1 ^{*,†}	P<0.01

Abbreviations: A, late diastolic mitral flow velocity; ADD, asymptomatic diastolic dysfunction; ANOVA, analysis of variance; BSA, body surface area; DHF, diastolic heart failure; DT, deceleration time; E, early diastolic mitral flow velocity; E', early diastolic mitral annular velocity; EF, ejection fraction; HT, hypertension; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; NS, not significant; PW, posterior wall; RV, right ventricular; S', systolic mitral annular velocity.

*P<0.05 relative to Control.

[†]P<0.05 relative to Simple HT.

[‡]P<0.05 relative to ADD.

Simple HT group. The E/E' was significantly higher in the Simple HT, ADD and DHF groups than in the Control group, and in the ADD and DHF groups compared with the Simple HT group. Neither E' nor E/E' significantly differed between the ADD and DHF groups (Table 2). Isovolumetric relaxation times in the ADD and DHF groups were significantly increased compared with those in the Control and Simple HT groups (Table 3).

Other echocardiography findings

Neither LV end-diastolic volume index nor LV end-systolic volume index significantly differed among the Control, Simple HT and ADD groups. However, these indices were significantly increased in DHF compared with the Control, Simple HT and ADD groups. The left atrial volume index in the ADD and DHF groups was significantly increased compared with those in the Control and Simple HT groups,

and in the DHF group compared with the ADD group. The LV wall thickness of the septum and posterior wall, relative wall thickness and LV mass index in the ADD and DHF groups were significantly increased compared with those in the Control and Simple HT groups, and LV mass index was significantly increased in the Simple HT group compared with the Control group. The Right ventricular pressure was significantly higher in the ADD group than that in the Control group, and in the DHF group compared with the Control and Simple HT groups (Table 2). The LV Tei index in the Simple HT, ADD and DHF groups was significantly higher than in the Control groups; the index in the ADD and DHF groups was significantly higher than in the Simple HT group; the index in the DHF group was significantly higher than in the ADD group (Table 3). Figures 4 and 5 show representative examples of ADD and DHF, respectively.

Reproducibility of measurements

The inter- and intra-observer variability of the LV ICT measurement was 2.3 ± 4.1 msec or $5.9 \pm 4.1\%$ of the mean value and 1.1 ± 0.1 msec or $2.9 \pm 2.9\%$, respectively.

DISCUSSION

We analyzed LV global and regional systolic function and diastolic function in patients with systemic HT to assess the relationship

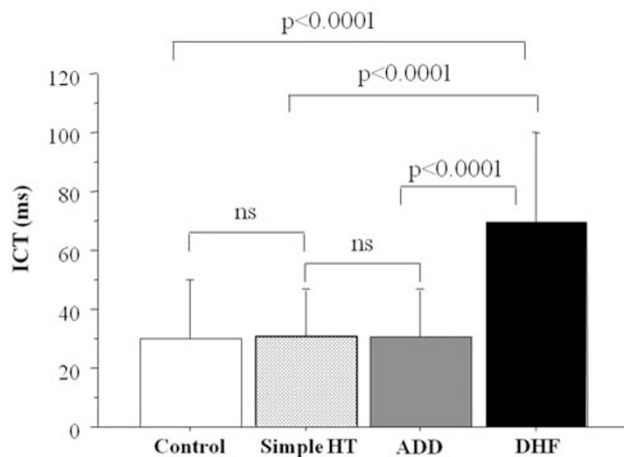


Figure 2 Comparison of isovolumetric contraction time (ICT) among four groups. ICT is significantly increased in diastolic heart failure (DHF) group compared with Control, simple hypertension (Simple HT) and asymptomatic diastolic dysfunction (ADD) groups, and does not significantly differ among the Control, Simple HT and ADD groups; NS, not significant.

between heart failure symptoms and cardiac function. We used EF, ICT and stroke volume as indices of global systolic function, and S' as an index of regional LV systolic function. Both global and regional LV systolic function significantly differed between the ADD and DHF groups. Regional systolic subtle dysfunction might develop before global LV systolic dysfunction and heart failure symptoms. These data suggest that LV global systolic dysfunction has a significant role in the development of heart failure symptoms in hypertensive patients with DHF.

The LV Tei index,^{15–18} which is a measure of global LV function, can be obtained before ICT analysis. The LV Tei index appeared to be sensitive in detecting combined LV diastolic and/or systolic dysfunction in our Simple HT, ADD and DHF patients.

LV global systolic function

The function, contractility and performance of the LV are important factors for LV global systolic function.³ We assessed EF as an indicator of LV function, ICT as a measure of LV contractility, and stroke volume to reflect LV performance. EF is a popular index of global systolic function and its value has been reported.¹⁹ However, EF expresses changes in the ratio of LV volume during ET and does not

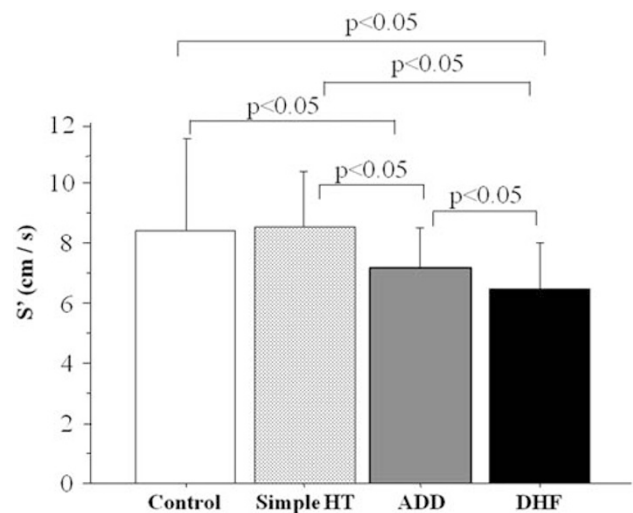


Figure 3 Comparison of systolic mitral annular velocity (S') among four groups. S' is significantly decreased in diastolic heart failure (DHF) compared with Control, simple hypertension (Simple HT) and asymptomatic diastolic dysfunction (ADD) groups, as well as in ADD, compared with Control and Simple HT groups.

Table 3 Cardiac time interval data

	Control (n=30)	Simple HT (n=131)	ADD (n=39)	DHF (n=50)	P-value by ANOVA
ET (ms)	286 ± 31	297 ± 36	298 ± 31	293 ± 38	NS
ICT (ms)	30 ± 19	31 ± 15	31 ± 16	70 ± 30 ^{*,†,‡}	P < 0.0001
ICT/ET	0.12 ± 0.09	0.10 ± 0.05	0.10 ± 0.05	0.24 ± 0.11 ^{*,†,‡}	P < 0.0001
IRT (ms)	88 ± 30	97 ± 25	116 ± 28 ^{†,§}	113 ± 32 ^{§,}	P < 0.0001
LV Tei index	0.39 ± 0.10	0.44 ± 0.13 [§]	0.50 ± 0.12 ^{§,}	0.64 ± 0.12 ^{*,†,¶}	P < 0.0001

Abbreviations: ADD, asymptomatic diastolic dysfunction; ANOVA, analysis of variance; DHF, diastolic heart failure; ET, ejection time; HT, hypertension; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; LV, left ventricular; NS, not significant.

^{*}P < 0.0001 relative to Control.

[†]P < 0.0001 relative to Simple HT.

[‡]P < 0.0001 relative to ADD.

[§]P < 0.05 relative to Control.

^{||}P < 0.05 relative to Simple HT.

[¶]P < 0.05 relative to ADD.

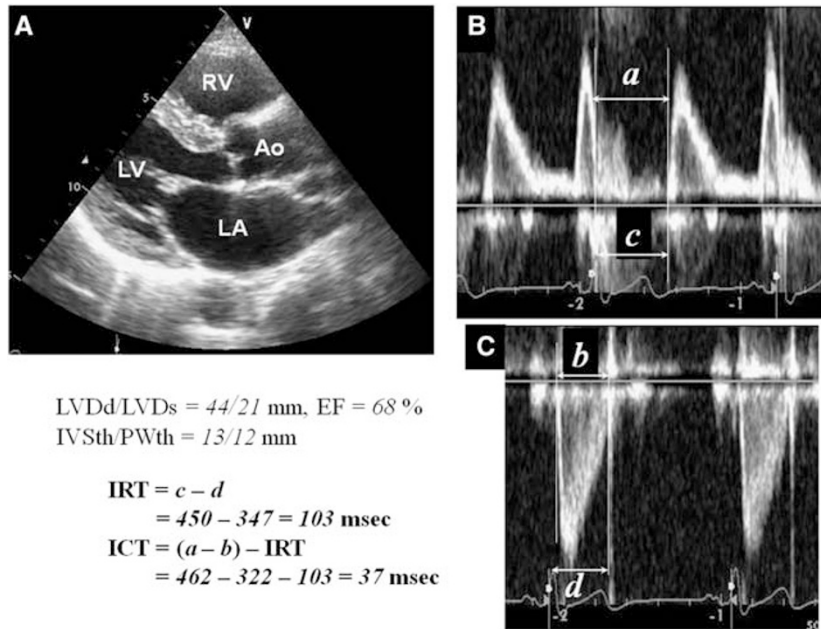


Figure 4 Two-dimensional long-axis (A), and pulsed wave Doppler mitral inflow velocity (B), and left ventricular outflow velocity (C), echocardiograms from a patient with hypertensive heart disease and asymptomatic diastolic dysfunction. Isovolumetric contraction time (ICT) is normal and isovolumetric relaxation time (IRT) has increased (see Figure 1 for details). Ao, aorta; Dd, diastolic dimension; Ds, systolic dimension; EF, ejection fraction; IVSth, interventricular septum thickness; PWth, posterior wall thickness; LA, left atrium; LV, left ventricle; RV, right ventricle.

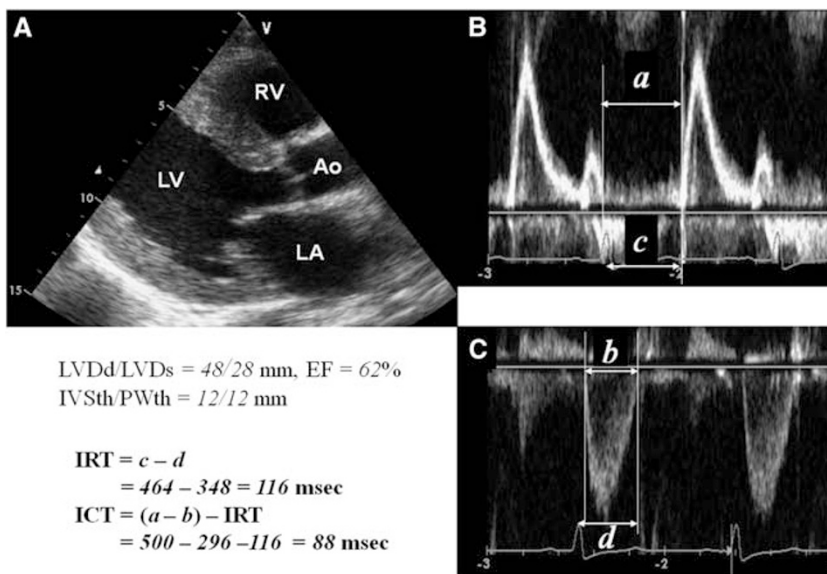


Figure 5 Two-dimensional long-axis (A), and pulsed wave Doppler mitral inflow velocity (B), and left ventricular outflow velocity (C), echocardiograms from a patient with hypertensive heart disease and diastolic heart failure. Both isovolumetric contraction and relaxation times have increased (see Figure 1 for details). Ao, aorta; Dd, diastolic dimension; Ds, systolic dimension; EF, ejection fraction; IVSth, interventricular septum thickness; PWth, posterior wall thickness; LA, left atrium; LV, left ventricle; RV, right ventricle.

reflect LV contractility. Thus, LV global systolic function cannot be assessed using EF alone, although the criteria for DHF in fact include this parameter as an index of global LV systolic function.^{20,21}

The LV ICT is an established index of LV contractility that correlates with the peak positive rate of the LV pressure increase.¹⁶ Yumoto *et al.*²² described the reliability of Doppler LV ICT as an index of fetal cardiac contractility. The LV ICT was noninvasively measured for the first time in 1962 using a phonocardiogram and carotid pulse.²³

Hirschfeld *et al.*²⁴ demonstrated the value of LV ICT for assessing systolic LV performance in various heart diseases using M-mode echocardiography. Pulsed Doppler echocardiography could reveal the beginning and end of mitral and aortic flow more clearly than M-mode echocardiography or phonocardiography, and thus improved LV ICT measurements. We regard ICT analysis as being simple, accurate and highly reproducible,²⁵ and it can be performed using any type of echocardiographic equipment.

LV global systolic dysfunction in DHF

He *et al.*⁶ identified global systolic dysfunction from LV pressure-volume findings in an animal model of DHF. Yoshida *et al.*⁷ analyzed the inertia force of late systolic aortic flow in a cardiac catheterization study and found that mild LV global systolic dysfunction is associated with DHF. Borlaug *et al.*¹⁰ analyzed circumferential mid-wall fractional shortening using echocardiography and found that myocardial contractility was impaired in hypertensive patients with heart failure and preserved EF. However, these studies did not assess the relationship between global systolic dysfunction and the development of heart failure symptoms in systemic HT.

Contrary to the current belief that LV remodeling does not occur in DHF, we found here that the LV end-diastolic volume index was significantly increased in the DHF group compared with the ADD group, although it fulfilled the diagnostic criteria for DHF, suggesting subtle LV remodeling. We excluded three hypertensive patients from the present study because they had reduced EF or LV enlargement suggesting the development of LV systolic dysfunction or LV remodeling. Maurer *et al.*²⁶ also described an increased LV diastolic diameter in 167 hypertensive patients with heart failure with a normal EF, a finding that is supported by our results. Rame *et al.*²⁷ reported that 18% of 159 patients with DHF developed reduced EF after a follow-up of ~4 years. Cahill *et al.*²⁸ also reported similar results. These data suggest that some DHF patients will develop systolic heart failure.

LV regional systolic dysfunction in DHF

Several studies have identified regional LV systolic longitudinal abnormalities in DHF using tissue Doppler imaging. Yu *et al.*⁴ reported the importance of LV systolic dysfunction in the development of DHF from ADD.

Because tissue Doppler measurements are affected by the Doppler angle, 2D speckle tracking methods have been developed that allow the quantitation of complex LV regional wall motion without interference from the angle. Wang *et al.*⁸ found preserved LV twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with DHF. They suggested that preserved LV twist and circumferential strain contributes to a normal EF in patients with DHF. The assessment of regional LV systolic function is apparently useful for understanding the pathophysiology of LV systolic dysfunction in DHF, but how regional LV systolic dysfunction contributes to the global LV systolic dysfunction and symptoms of heart failure remains unknown.

LV diastolic dysfunction in DHF

Many investigators have proposed that the predominant pathophysiological mechanism of heart failure in DHF is abnormal LV diastolic function. However, we did not identify any significant differences in the degree of LV diastolic dysfunction between the ADD and DHF groups.

Limitations

We did not use 2D speckle tracking to assess regional LV function. This method might have clarified precise wall motion changes in various directions in patients with DHF. However, we analyzed LV longitudinal deformation, which is an important index of 2D speckle tracking, and differences in the abilities of Doppler and 2D speckle tracking to detect LV longitudinal deformation have not yet been clarified.

Conclusions

LV global systolic dysfunction appears to have a significant role in the development of DHF in patients with systemic HT. Comprehensive

assessment of global LV systolic function seems to be important for understanding the pathophysiology of heart failure in DHF.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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