Original Article

Hemodynamic Characteristics of Patients with Diastolic Heart Failure and Hypertension

Naoki FUJIMOTO[1)], Katsuya ONISHI[2)], Kaoru DOHI[1)], Masaki TANABE[1)], Tairo KURITA[1)], Takeshi TAKAMURA[1)], Norikazu YAMADA[1)], Tsutomu NOBORI[2)], and Masaaki ITO[1)]

Diastolic heart failure (DHF) has different underlying pathophysiologic mechanisms. We sought to compare hemodynamic characteristics in DHF patients with or without hypertension. A conductance catheter with microtip-manometer was used to measure left ventricular (LV) function and hemodynamics in 28 DHF patients. After baseline measurements, nitroglycerin was infused to alter the loading condition and the measurements were repeated. At baseline, end-systolic pressure was higher and the time constant of LV relaxation (τ) was longer in hypertensive DHF patients. Patients in hypertensive DHF had lower LV-arterial coupling ratio than those in non-hypertensive DHF. The peak of loading sequence was in early systole in non-hypertensive DHF patients and in late systole in hypertensive DHF patients. Nitroglycerin decreased LV end-systolic pressure and end-diastolic volume in both groups. In non-hypertensive DHF, nitroglycerin significantly reduced stroke volume and shortened τ (59±11 *vs.* 54±10 ms, $p<0.05$) without any changes in the time to peak LV force, effective arterial elastance (E_a), or LV-arterial coupling ratio. In contrast, in hypertensive DHF patients, nitroglycerin significantly reduced E_a and shortened the time to peak LV force, resulting in an improved LV-arterial coupling ratio, preserved stroke volume and shortened τ (75±14 *vs.* 62±13 ms, $p<0.05$). In conclusion, LV relaxation was more prolonged in hypertensive DHF patients than non-hypertensive DHF patients, partly because of the different loading sequence. Changing the loading condition by nitroglycerin improved LV systolic and diastolic function in hypertensive DHF patients. (*Hypertens Res* 2008; 31: 1727–1735)

***Key Words*: diastolic heart failure, hypertension, hemodynamics**

Introduction

Patients suffering from diastolic heart failure (DHF) must meet the following 3 criteria: 1) evidence of congestive heart failure, 2) normal left ventricular (LV) systolic function, and 3) evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness (*1*, *2*). DHF is a clinically heterogeneous syndrome, and patients may have different underlying pathophysiological mechanisms such as myocardial hypertrophy, fibrosis, hypertension, ischemia, diabetes mellitus, or infiltrative cardiomyopathies such as amyloidosis. Therefore, DHF patients might be expected to respond quite differently to therapeutic interventions (*3–6*). Patients with DHF are generally elderly women with increased LV mass and a history of hypertension (*7–10*). Hypertension plays an important role in DHF, and late systolic load in hypertension has been reported to cause afterload-dependent relaxation delay (*11–13*). However, hemodynamic characteristics of patients with DHF with or without hypertension have not been compared. It has been shown that NO donors that enhance NO release improve diastolic function partly by changing the systolic loading sequence in patients with excessive arterial load (*11*). Therefore, using conductance methods

From the [1)]Department of Cardiology and [2)]Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Japan.

Address for Reprints: Katsuya Onishi, M.D., Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, 2–174 Edobashi, Tsu 514–8507, Japan. E-mail: katsu@clin.medic.mie-u.ac.jp

Received January 11, 2008; Accepted in revised form July 2, 2008.

Table 1. Patient Characteristics

	Hypertensive DHF (n=16)	Non-hypertensive DHF (n=12)	p
Age, years	73±8	60±10	0.002
Gender, % male	62	58	0.58
Body surface area, m^2	1.6±0.2	1.5±0.1	0.49
Body mass index, kg/m^2	22±3	21±2	0.61
Systolic blood pressure, mmHg	147±20	110±15	0.001
Diastolic blood pressure, mmHg	70±12	61±10	0.048
Two dimension echo			
Ejection fraction, %	55±7	59±8	0.20
Left ventricular hypertrophy, *n* (%)	9 (57)	2 (17)	0.04
Left ventricular mass index, g/m^2	158±47	120±22	0.009
Comorbidities, *n* (%)			
Coronary heart disease	9 (57)	8 (67)	0.58
Diabetes mellitus	6 (38)	7 (58)	0.28
Hemoglobin A1c, %	5.8±2.4	5.9±2.8	0.93
Serum hemoglobin, g/dL	11.7±2.0	11.9±1.6	0.71
BNP, pg/mL	201±267	121±113	0.29
Concurrent medication, *n* (%)			
ACE-inhibitors/AII-antagonists	11 (69)	3 (25)	0.02
β-Blockers	11 (69)	1 (8)	0.002
Calcium channel blockers	4 (25)	0 (0)	0.11
Diuretics	3 (19)	2 (17)	1.00
Insulin	0 (0)	1 (8)	0.24
Oral antidiabetic drugs	4 (25)	2 (17)	0.77

DHF, diastolic heart failure; BNP, brain natriuretic peptide; ACE, angiotensin converting enzyme; AII, angiotensin II. Values are mean±SD values. p values are for the group with hypertensive DHF *vs*. non-hypertensive DHF.

that can provide LV stiffness, LV relaxation, and loading sequence, we evaluated the hemodynamic differences between DHF patients with or without hypertension. We also evaluated the effects of altering the loading condition using nitroglycerin on LV systolic and diastolic function and hemodynamics.

Methods

Study Groups

Twenty-eight patients (17 men and 11 women, aged 67±11 years) with DHF who had been admitted to Mie University Hospital were enrolled in this study. They either belonged to the New York Heart Association symptomatic heart failure functional classes II to IV or were referred for cardiac catheterization to assess dyspnea. After the symptoms of heart failure had been relieved by therapy including diuretics, vasodilators, and β-blockers, cardiac catheterization was performed. The diagnosis of DHF was made if 2 criteria were present: 1) symptoms and signs of heart failure and 2) LV ejection fraction >50%, obtained by echocardiography upon admission. Seventeen patients had a past history of coronary artery disease, and most of them suffered from mild myocardial infarction. Patients were excluded from this study if they had residual ischemia in their coronary artery by perfusion MRI, valvular heart disease, atrial fibrillation, regional wall-motion abnormalities, or restriction/constriction (based on right/left heart catheterization). All intravenous medications were discontinued at least 7 d before cardiac catheterization. Patients had been receiving diuretics (n=5), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (n=14), β-blockers (n=12), and calcium channel blockers (n=4) before enrollment in the study (Table 1). All medications were withheld for at least 48 h before cardiac catheterization, except for diuretics. The average LV ejection fraction was 57±7% (range 51–72%), and their mean plasma brain natriuretic peptide (BNP) level was 167±216 pg/mL (normal range <18 pg/mL). Written informed consent was obtained from all patients, and the protocol was approved for use by the Human Studies Subcommittee of Mie University Graduate School of Medicine.

Cardiac Catheterization Procedures

Patients underwent routine right and left heart catheterization,

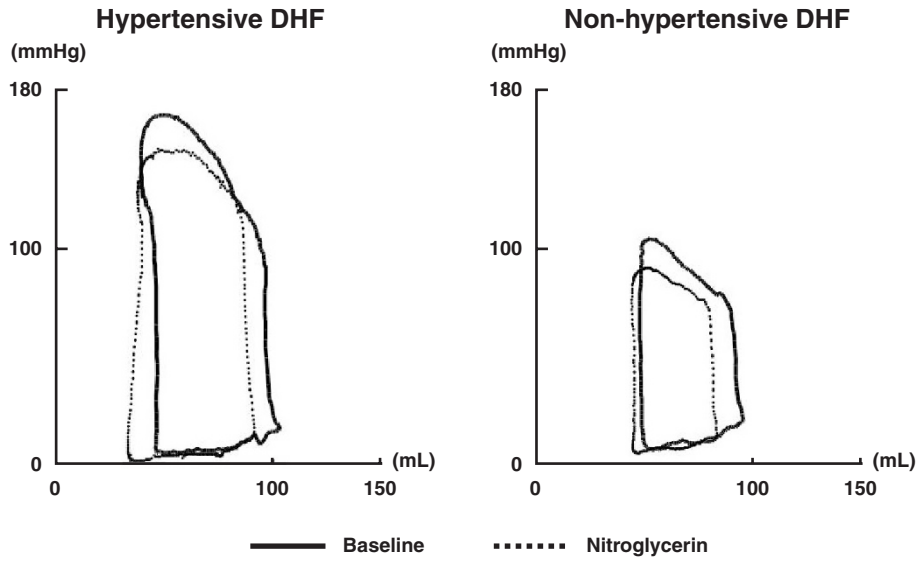

Fig. 1. *Representative LV pressure-volume loops from patients in hypertensive DHF and non-hypertensive DHF before and after nitroglycerin administration.*

left ventriculography and coronary angiography. A non-ionic contrast agent was used to minimize the potential negative inotropic effects of the contrast medium. A 6F single-field conductance catheter (Webster Laboratories, Baldwin Park, USA) with a 2F microtip manometer (Millar Instruments, Inc., Houston, USA) placed within its lumen was advanced to a LV apex and connected to a digital stimulator microprocessor (Sigma V [dual-field system]; Leycom, Zoetermeer, The Netherlands) to measure LV volume. The conductance catheter technique and its principles have been fully described previously (*4*, *13*, *14*). Real-time pressure-volume diagram generation and analog/digital conversion (333 Hz) were performed using a 16-bit microcomputer system (PC-9801VX, NEC Co., Tokyo, Japan). At the beginning of the study, the conductance catheter signal gain was calibrated using a thermodilution-derived stroke volume. A calibration offset (parallel conductance) was corrected by matching a conductance catheter signal at end-diastole with an end-diastolic volume measured by biplane ventriculography using an area-length method.

Study Protocol

Three sets of steady-state LV pressure-volume loops were recorded over a 12-s recording period. Arterial blood samples were collected for measurement of plasma BNP concentrations. After baseline data were measured, nitroglycerin was infused intravenously at a dose of 0.3–0.5 μg/kg/min to decrease systolic arterial pressure by around 20 mmHg. Fifteen minutes after nitroglycerin infusion, 3 sets of steady-state pressure-volume loops were recorded again.

Data Analysis

Steady-state hemodynamic measurements were determined from signal-averaged cardiac cycles, combining 5 to 10 sequential beats. Stroke volume was calculated as end-diastolic minus end-systolic volume. The monoexponential-based time constant of isovolumetric fall of LV pressure was calculated with the assumption that pressure decayed to a non-zero asymptote (*15*). The LV contractile state was assessed by end-systolic elastance (E_{es}) using a single-beat formula, which is sensitive to changes in contractile state but relatively insensitive to changes in loading conditions (*16*). Effective arterial elastance (E_a) was calculated as end-systolic pressure divided by stroke volume (*17*). The LV-arterial coupling ratio was calculated as E_a divided by E_{es}. The total systemic resistance was calculated as end-systolic pressure divided by cardiac output (*14*). The diastolic pressure-volume relation was described by an exponential equation, $P=Ae^{\beta V}$, where P is the LV pressure, V is the LV volume, A is a curve fitting constant, and β is a stiffness constant used to quantify passive stiffness (*18*). The LV total circumferential force (TCF) was calculated from (*19*):

$$\text{TCF} = 1.64 \times \text{LV pressure} \times \text{LV volume}^{2/3}.$$

To assess loading conditions and sequences, the time from end diastole to the peak of the force was obtained.

Statistical Analysis

Data in the text and table are expressed as mean±SD. Baseline characteristics of patients were compared using unpaired *t*-tests for quantitative variables and the Fisher exact test for

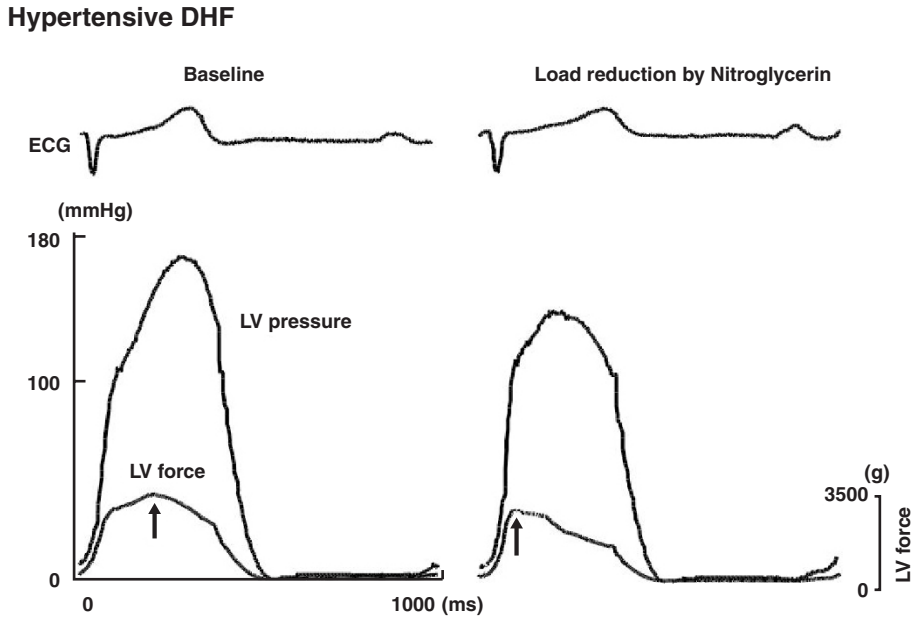

Fig. 2. *Traces showing LV force profile and LV pressure during systole in a representative patient in hypertensive DHF.*

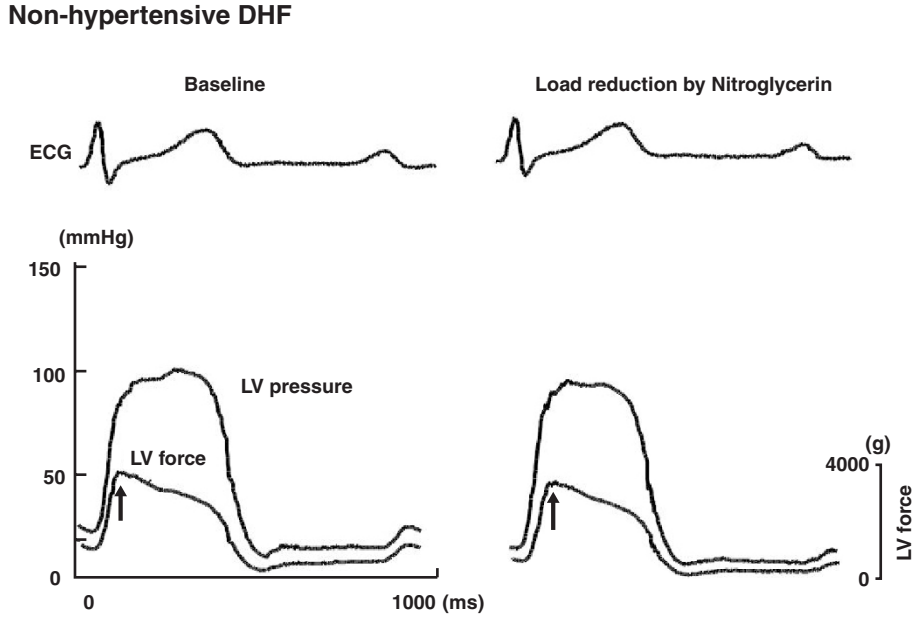

Fig. 3. *Traces showing LV force profile and LV pressure during systole in a representative patient in non-hypertensive DHF.*

categorical variables. The differences in hemodynamic variables before and after administration of intravenous nitroglycerin were tested by 2-way repeated ANOVA measurements with a Student-Newman-Keuls test. p values <0.05 were considered to be statistically significant.

Results

Patients' Subset Stratification

Patients were stratified into 2 groups: hypertensive DHF and

Table 2. Hemodynamic and Conductance Volume Measurements

	Hypertensive DHF	Non-hypertensive DHF	*p*
Heart rate, bpm			
Baseline	62±9	66±10	0.69
Nitroglycerin	63±9	68±10	0.61
LV end-systolic pressure, mmHg			
Baseline	133±20	106±15	0.02
Nitroglycerin	114±20*	89±14*	0.04
LV end-diastolic pressure, mmHg			
Baseline	17±4	17±5	0.71
Nitroglycerin	11±4*	10±4*	0.67
LV end-diastolic volume, mL			
Baseline	115±36	119±44	0.87
Nitroglycerin	105±31*	108±44*	0.89
LV end-systolic volume, mL			
Baseline	53±19	49±18	0.63
Nitroglycerin	42±16*	45±17*	0.81
Stroke volume, mL			
Baseline	62±21	70±30	0.94
Nitroglycerin	62±21	63±30*	0.92
Ejection fraction, %			
Baseline	56±7	59±8	0.66
Nitroglycerin	61±9*	58±10	0.82
E_{es}, mmHg/mL			
Baseline	2.3±1.1	2.2±1.1	0.80
Nitroglycerin	2.6±1.3	2.2±1.2	0.92
E_a, mmHg/mL			
Baseline	2.4±0.9	1.8±0.8	0.39
Nitroglycerin	2.0±0.8*	1.7±0.8	0.77
E_a/E_{es}			
Baseline	1.1±0.3	0.8±0.2	0.02
Nitroglycerin	0.9±0.3*	0.9±0.3	0.89
Peak of TCF, g			
Baseline	3,718±1,037	3,151±1,011	0.50
Nitroglycerin	3,103±832*	2,959±923*	0.78
Time to peak TCF, ms			
Baseline	253±48	142±27	<0.001
Nitroglycerin	181±54*	133±20	0.07
τ, ms			
Baseline	75±14	59±11	0.04
Nitroglycerin	62±13*	54±10*	0.44
Curve-fitting constant			
Baseline	1.4±1.4	1.1±1.7	0.80
Nitroglycerin	1.0±1.0	1.1±1.8	0.94
Stiffness constant			
Baseline	0.027±0.015	0.032±0.015	0.85
Nitroglycerin	0.031±0.016	0.032±0.018	0.99

DHF, diastolic heart failure; LV, left ventricular; peak of TCF, the peak value of LV total circumferential force (TCF); time to peak TCF, the time from end-diastole to the peak of TCF during LV ejection; τ, time constant of pressure decay; E_{es}, LV end-systolic elastance; E_a, effective arterial elastance. Values are mean±SD values. *p* values are for the group with hypertensive DHF *vs*. non-hypertensive DHF. *$p<0.05$ indicates statistically significant changes from baseline for comparison of the effects of nitroglycerin.

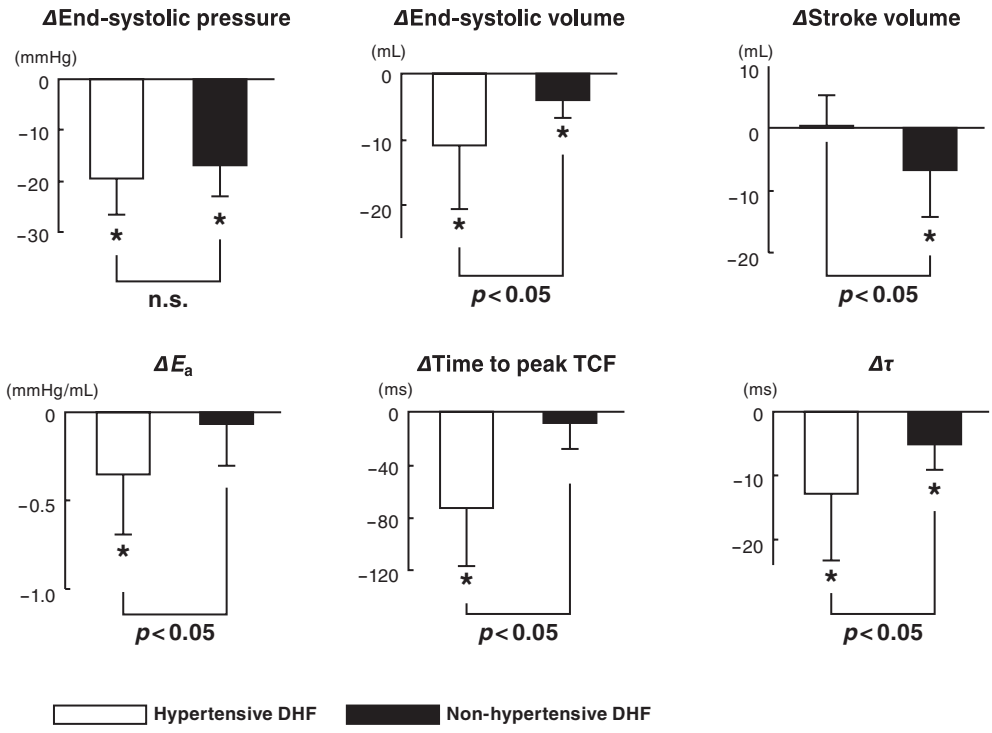

Fig. 4. *Bar graphs showing changes in end-systolic pressure (ΔEnd-systolic pressure), end-systolic volume (ΔEnd-systolic volume), stroke volume (ΔStroke volume), effective arterial elastance (ΔE_a), time to peak TCF (ΔTime to peak TCF), and time constant of LV relaxation ($\Delta\tau$) after nitroglycerin infusion. *$p < 0.05$ vs. baseline.*

non-hypertensive DHF. Hypertensive DHF ($n=16$) was defined as patients who, upon admission, had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or a reported history of hypertension. Non-hypertensive DHF ($n=12$) was defined as patients without a reported history of hypertension and whose systolic blood pressure was <140 mmHg and diastolic blood pressure <90 mmHg upon admission. Accordingly, systolic and diastolic blood pressures were higher in hypertensive DHF patients than in non-hypertensive DHF patients (Table 1). Patients with hypertensive DHF had female/male distributions similar to those of non-hypertensive DHF patients but were older than non-hypertensive DHF patients (73±8 *vs*. 60±10 years). The number of patients with LV hypertrophy by 2-D echocardiogram was higher in hypertensive DHF than in non-hypertensive DHF, although there were no significant differences in body surface area, body mass index, or history of coronary artery disease or diabetes mellitus. There were no significant differences between groups in mean plasma BNP levels, hemoglobin A1c levels, LV ejection fraction, or prescription of antidiabetic drugs.

Baseline Hemodynamic Characteristics

Representative data of LV pressure-volume loops and the relation between LV pressure and the loading sequence are shown in Figs. 1–3. At baseline, LV end-diastolic pressure was elevated in the both groups, while LV end-systolic pressure was higher in hypertensive DHF patients than in non-hypertensive DHF patients (Fig. 1). The systolic loading sequence peaked in late systole in the hypertensive DHF group but in early systole in the non-hypertensive DHF group (Figs. 2, 3).

LV function and hemodynamic characteristics are summarized in Table 2. There were no significant differences in heart rate, LV end-diastolic and end-systolic volume, stroke volume, E_{es}, or E_a between the two groups. The LV-arterial coupling ratio in hypertensive DHF patients was poorer than that in non-hypertensive DHF patients (1.1±0.3 *vs*. 0.8±0.2, $p=0.02$). τ was longer in the hypertensive DHF group than in the non-hypertensive DHF group (75±14 *vs*. 59±11 ms), and the time to peak TCF in hypertensive DHF patients was longer than in non-hypertensive DHF patients (253±48 *vs*. 142±27 ms). There were no significant differences in LV stiffness assessed by curve-fitting constant and stiffness constant between the two groups.

Effect of Nitroglycerin on Cardiac Function and Hemodynamics

LV pressure-volume loops shifted downward and leftward in both groups (Fig. 1). The systolic loading sequence in hypertensive DHF patients demonstrated a dramatically altered

peak from late systole to early systole, whereas no change was seen in non-hypertensive DHF patients (Figs. 2, 3). Changes in LV function and hemodynamic characteristics by nitroglycerin are summarized in Table 2. The heart rate was not statistically affected by nitroglycerin in either group. LV end-systolic and end-diastolic pressure and end-diastolic volume were decreased to the same extent in both groups. LV end-systolic volume decreased in both groups, but the degree of the decrease was smaller in hypertensive DHF patients than in non-hypertensive DHF patients (Fig. 4), resulting in the preserved stroke volume (62±21 *vs*. 62±21 mL) and improved ejection fraction in hypertensive DHF patients. By contrast, the stroke volume in the non-hypertensive DHF group was decreased by nitroglycerin treatment (70±30 *vs*. 63±30 mL). E_a decreased in the hypertensive DHF group (2.4±0.9 *vs*. 2.0±0.8 mmHg/mL), while there was no change in non-hypertensive DHF group. In non-hypertensive DHF patients, nitroglycerin decreased τ by 9% (59±11 *vs*. 54±10 ms) without changing the time to peak TCF and LV-arterial coupling ratio. Conversely, in hypertensive DHF patients, nitroglycerin shortened τ by 18% (75±14 *vs*. 62±13 ms), shortened time to peak TCF (253±48 *vs*. 181±54 ms), and improved LV-arterial coupling ratio. The improvement in LV relaxation was greater in hypertensive DHF patients than non-hypertensive DHF patients (Fig. 4). Nitroglycerin displaced the diastolic pressure-volume relation downward and leftward, but had no significant effects on LV stiffness in both groups.

Discussion

In the present study, we examined the characteristics of cardiac function and hemodynamics and their responses to nitroglycerin in DHF patients with or without hypertension by using pressure-volume loops. At baseline, LV relaxation was more impaired in hypertensive DHF patients than in non-hypertensive DHF patients. Nitroglycerin shortened LV relaxation and preserved stroke volume due to the changed loading sequence and improved LV-arterial coupling ratio in patients with hypertensive DHF.

The present results are consistent with the previous studies showing that LV relaxation was impaired in patients with hypertensive DHF compared with disease-free control subjects (*18*). The excessive arterial elastance would contribute to the prolonged LV relaxation in hypertensive DHF patients. Changing the loading sequence would affect LV relaxation because LV relaxation was sensitive to late systolic load, but not to the load itself (*12*, *20*). We previously reported that nitroglycerin altered the peak of the loading sequence from late to early systole, which partly contributed to the shortening of LV relaxation in excessive arterial elastance (*11*). Consistent with the previous report, the peak of LV force was in late systole at baseline and nitroglycerin changed the peak of the loading sequence from late to early systole in DHF patients with hypertension. With an early increase in systolic load, calcium availability is adequate to permit recruitment of additional cross-bridge formation, so the resultant stress on individual cross-bridges does not change. However, with late load increases, the availability of calcium is reduced to limit the formation of additional cross-bridges, so the stress on individual cross-bridges increases, which may delay cross-bridge interaction and slow the rate of the subsequent fall in left ventricular pressure (*21*). The effect of elastic recoil on LV relaxation should be considered (*22*). Nitroglycerin decreased LV end-systolic volume in hypertensive DHF patients more than in non-hypertensive DHF patients (11 *vs*. 4 mL, $p<0.05$), suggesting that elastic recoil might contribute to the shortening of LV relaxation to a greater extent in hypertensive DHF than non-hypertensive DHF (Fig. 4). The difference of LV mass might affect LV relaxation at baseline. Intracoronary NO donors improved diastolic relaxation in normal subjects, while the hypertrophied ventricle shows no effect of intracoronary NO donors on LV contraction and relaxation (*23*, *24*). In the present study, nitroglycerin shortened LV relaxation in hypertensive DHF patients to a greater extent than non-hypertensive DHF patients, although the hypertensive DHF group exhibited more LV hypertrophy. Extrinsic, but not intrinsic, factors may affect the improvement of LV relaxation during nitroglycerin infusion.

Stroke volume was preserved during nitroglycerin infusion in hypertensive DHF patients despite a decrease in preload assessed by LV end-diastolic volume. Haber *et al*. showed that patients with excessive arterial elastance exhibited a predominant afterload reduction without a decrease in stroke volume in response to nitroglycerin (*25*). Consistent with the previous study, we observed a preserved stroke volume in hypertensive DHF patients during nitroglycerin infusion. The effect of decreased E_a on stroke volume would overcome that of LV preload reduction during nitroglycerin infusion. By contrast, in non-hypertensive DHF patients, nitroglycerin had no effects on E_{es}, E_a, and LV-arterial coupling, resulting in a decreased stroke volume due mainly to preload reduction.

In the present study, we observed that LV diastolic stiffness was unchanged by nitroglycerin in both groups. Paulus *et al*. reported that the presence of an NO donor improved LV stiffness accompanied with a slight increase in end-diastolic volume and a lowered end-diastolic pressure (*26*). The discrepancy of LV stiffness during nitroglycerin infusion may be due to the extrinsic forces applied by the pericardium and the right side of the heart. Because the right ventricle faces the left ventricle, elevation of right heart diastolic pressures can constrain the filling of the left ventricle, and reduction of the right heart diastolic pressure by nitroglycerin may unload the septum and improve LV distensibility (*5*). Thus, a calculated LV stiffness might be improved partly because of reduced external constraint by nitroglycerin. The average LV end-diastolic volume was smaller (117±39 *vs*. 158±34 mL), and LV end-diastolic pressure was lower, in the present study than in the previous study, suggesting a smaller contribution of external constraints.

Limitations

First, the present study was performed after patients had been treated and their symptoms were relieved. It is possible that diastolic parameters and ventricular and arterial properties at the time of catheterization were different from those upon admission. Furthermore, patients were stratified into hypertensive or non-hypertensive DHF according to the blood pressure upon admission and/or a reported history of hypertension. Therefore, we cannot deny the past history of hypertension in patients with non-hypertensive DHF.

Second, we noticed low LV end-diastolic pressure. In the present study, symptoms of heart failure were relieved after treatment with diuretics and nitrates, which improved pulmonary congestion. Although we discontinued the use of nitrates at least 7 d before the procedures, diuretics were appropriately used to treat heart failure, which may cause the low LV end-diastolic pressure at baseline.

Third, we cannot neglect the effect of autonomic reflexes after nitroglycerin infusion on LV function and hemodynamics, although the heart rate was relatively constant.

Finally, the limitations of the conductance catheter have already been acknowledged. Volume calibration was based on ventriculography, which is error-prone. However, most of the analysis required only that the same calibration be applied to both ventricular and vascular parameter data.

Conclusions

In the present study, we demonstrated the different cardiac function and hemodynamics and the response to nitroglycerin between DHF patients with and without hypertension. We clearly showed that the decrease in arterial elastance was an important factor to treat hypertensive DHF, but not non-hypertensive DHF. The present data support the conclusion that DHF is a clinically heterogeneous syndrome because of different underlying pathophysiologic mechanisms. Further studies are needed to determine therapeutic options that can adjust to underlying pathophysiologic mechanisms.

References

1. Vasan RS, Levy D: Defining diastolic heart failure: a call for standardized diagnostic criteria. *Circulation* 2000; **101**: 2118–2121.
2. European Study Group on Diastolic Heart Failure: Working Group Report. How to diagnose diastolic heart failure. *Eur Heart J* 1998; **19**: 990–1003.
3. Maurer MS, King DL, El-Khoury Rumbarger, Packer M, Burkhoff D: Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. *J Card Fail* 2005; **11**: 177–187.
4. Yamanaka T, Onishi K, Tanabe M, *et al*: Force- and relaxation-frequency relations in patients with diastolic heart failure. *Am Heart J* 2006; **152**: 966e1–966e7.
5. Little WC, Brucks S: Therapy for diastolic heart failure. *Prog Cardiovasc Dis* 2005; **47**: 380–388.
6. Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation* 2002; **105**: 1503–1508.
7. Kitzman DW, Little WC, Brubaker PH, *et al*: Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA* 2002; **288**: 2144–2150.
8. Kitzman DW, Gardin JM, Gottdiener JS, *et al*: Importance of heart failure with preserved systolic function in patients > or = 65 years of age. CHS Research Group. Cardiovascular Health Study. *Am J Cardiol* 2001; **87**: 413–419.
9. Zile MR, Brutsaert DL: New concepts in diastolic dysfunction and diastolic heart failure. Part I: Diagnosis, prognosis, and measurements of diastolic function. *Circulation* 2002; **105**: 1387–1393.
10. Klapholz M, Maurer M, Lowe AM, *et al*: Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol* 2004; **43**: 1432–1438.
11. Fujimoto N, Onishi K, Tanabe M, *et al*: Nitroglycerin improves left ventricular relaxation by changing systolic loading sequence in patients with excessive arterial load. *J Cardiovasc Pharmacol* 2005; **45**: 211–216.
12. Hori M, Inoue M, Kitakaze M, *et al*: Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. *Am J Physiol* 1985; **249**: H747–H754.
13. Little WC, Cheng CP, Peterson T, Vinten-Johansen J: Response of the left ventricular end-systolic pressure-volume relation in conscious dogs to a wide range of contractile states. *Circulation* 1988; **78**: 736–745.
14. Mizuno O, Onishi K, Dohi K, *et al*: Effects of therapeutic doses of human atrial natriuretic peptide on load and myocardial performance in patients with congestive heart failure. *Am J Cardiol* 2001; **88**: 863–866.
15. Raff GL, Glantz SA: Volume loading slows left ventricular isovolumic relaxation rate. *Circ Res* 1981; **48**: 813–824.
16. Shishido T, Hayashi K, Shigemi K, Sato T, Sugimachi M, Sunagawa K: Single-beat estimation of end-systolic elastance using bilinearly approximated time-varying elastance curve. *Circulation* 2000; **102**: 1983–1989.
17. Kelly RP, Ting CT, Yang TM, *et al*: Effective arterial elastance as index of arterial vascular load in humans. *Circulation* 1992; **86**: 513–521.
18. Zile MR, Baicu CF, Gaasch WH: Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; **350**: 1953–1959.
19. Suga H, Sagawa K: Graphical estimation of ventricular wall force and stress from pressure-volume diagram. *Am J Physiol* 1979; **236**: 787–789.
20. Gillebert TC, Leite-Moreira AF, De Hert SG: Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 2000; **5**: 345–355.
21. Ishizaka S, Asanoi H, Wada O, Kameyama T, Inoue H: Loading sequence plays an important role in enhanced load sensitivity of left ventricular relaxation in conscious dogs with tachycardia-induced cardiomyopathy. *Circulation* 1995; **92**: 3560–3567.
22. Firstenberg MS, Smedira NG, Greenberg NL, *et al*: Relationship between early diastolic intraventricular pressure

gradients, an index of elastic recoil, and improvements in systolic and diastolic function. *Circulation* 2001; **104**: I330–I335.
23. Shah AM, Spurgeon HA, Sollott SJ, Talo A, Lakatta EG: 8-Bromo-cGMP reduces the myofilament response to Ca^{2+} in intact cardiac myocytes. *Circ Res* 1994; **74**: 970–978.
24. Matter CM, Mandinov L, Kaufmann PA, Vassalli G, Jiang Z, Hess OM: Effect of NO donors on LV diastolic function in patients with severe pressure-overload hypertrophy. *Circulation* 1999; **99**: 2396–2401.
25. Haber HL, Simek CL, Bergin JD, *et al*: Bolus intravenous nitroglycerin predominantly reduces afterload in patients with excessive arterial elastance. *J Am Coll Cardiol* 1993; **22**: 251–257.
26. Paulus WJ, Vantrimpont PJ, Shah AM: Acute effects of nitric oxide on left ventricular relaxation and diastolic distensibility in humans. Assessment by bicoronary sodium nitroprusside infusion. *Circulation* 1994; **89**: 2070–2078.