Combined Ventricular Systolic and Arterial Stiffening in Patients With Heart Failure and Preserved Ejection Fraction

Implications for Systolic and Diastolic Reserve Limitations

Miho Kawaguchi, MD; Ilan Hay, MD; Barry Fetics, MSE; David A. Kass, MD

Background—Heart failure with preserved ejection fraction (HF-nlEF) is common in aged individuals with systolic hypertension and is frequently ascribed to diastolic dysfunction. We hypothesized that such patients also display combined ventricular-systolic and arterial stiffening that can exacerbate blood pressure lability and diastolic dysfunction under stress.

Methods and Results—Left ventricular pressure-volume relations were measured in patients with HF-nlEF (n = 10) and contrasted with asymptomatic age-matched (n = 9) and young (n = 14) normotensives and age- and blood pressure-matched controls (n = 25). End-systolic elastance (stiffness) was higher in patients with HF-nlEF (4.7 ± 1.5 mm Hg/mL) than in controls (2.1 ± 0.9 mm Hg/mL for normotensives and 3.3 ± 1.0 mm Hg/mL for hypertensives; P < 0.001). Effective arterial elastance was also higher (2.6 ± 0.5 versus 1.9 ± 0.5 mm Hg/mL) due to reduced total arterial compliance; the latter inversely correlated with end-systolic elastance (P < 0.0001). Body size and stroke volumes were similar and could not explain differences in ventricular-arterial stiffening. HF-nlEF patients also displayed diastolic abnormalities, including higher left ventricular end-diastolic pressures (24.3 ± 4.6 versus 12.9 ± 5.5 mm Hg), caused by an upward-shifted diastolic pressure-volume curve. However, isovolumic relaxation and the early-to-late filling ratio were similar in age- and blood pressure-matched controls. Ventricular-arterial stiffening amplified stress-induced hypertension, which worsened diastolic function, and predicted higher cardiac energy costs to provide reserve output.

Conclusion—Patients with HF-nlEF have systolic-ventricular and arterial stiffening beyond that associated with aging and/or hypertension. This may play an important pathophysiological role by exacerbating systemic load interaction with diastolic function, augmenting blood pressure lability, and elevating cardiac metabolic demand under stress. (Circulation. 2003;107:714-720.)

Key Words: heart failure ■ diastole ■ compliance ■ aging ■ hypertension
The present study used pressure-volume (PV) analysis to test the hypothesis that HF-nlEF patients have increased systolic-ventricular and vascular stiffening above that predicted by age, body size, heart volume, and blood pressure. We further directly examined diastolic PV relations to clarify mechanisms of diastolic dysfunction and to provide experimental and theoretic analysis to support a role for coupled ventricular-arterial stiffening in limiting both systolic and diastolic reserve.

Methods

Study Population

Four patient groups were studied. HF-nlEF patients (n=10) had chronic NYHA class II/III symptoms responsive to diuretics and were referred for cardiac catheterization to assess dyspnea, with 6 having a recent hospitalization for rapid-onset pulmonary edema. None had significant coronary artery or valvular disease, regional wall-motion abnormalities, or restriction/constriction (as based on right/left heart catheterization). EF was >50% (echo or ventriculogram) within 72 hours of symptoms. Left ventricular hypertrophy (LVH) was not required but was confirmed in 6 subjects (cardiac mass/body surface area ≥125g/m² and/or mean wall thickness >1.1 cm²). LVH was not definitively ascertained in 2 subjects, although neither had LVH by history, prior echocardiograms, or ECG.

Three nonfailure control groups were also studied: those <50 years with normal LV function (n=9; age-matched controls); those ≥50 years with normal LV function (n=9; age-matched normotensive controls); and those ≥50 years with hypertension (systolic blood pressure >140 mm Hg; pulse pressure >60 mm Hg; n=25; CON-HTN). All but CON-HTN groups underwent invasive PV analysis by conductance/micromanometer catheter. Invasive studies (all groups) were performed between 1987 and 2001, with all patients fulfilling appropriate entry criteria used for analysis. Some of these data have been previously reported in other studies and contexts. Young and age-matched control subjects were referred for atypical chest pain syndrome and had insignificant coronary artery disease, no LVH or valvular disease, and normal EF. CON-HTN subjects also had no history of coronary artery or myocardial disease. They were assessed noninvasively as part of a recent pharmacology study.

Invasive PV Analysis

PV catheterization was performed as described previously. The volume signal was calibrated by matching catheter to thermodilution cardiac output and catheter to ventriculogram EF. This minimizes absolute volume image-estimation errors and couples thermodilution to simultaneous catheter data. Data were obtained at rest and during preload reduction via balloon obstruction of inferior vena caval inflow (NuMed). In 8 controls and 6 HF-nlEF patients, PV data were also obtained after sustained handgrip exercise (n=11; 2 to 5 minutes) or supine bicycle exercise (n=3; 3 to 10 minutes).

Noninvasive Analysis

CON-HTN subjects were not referred for catheterization, so data were obtained noninvasively. LV end-systolic elastance (Ees) was derived from arm-cuff pressures, echo-Doppler derived stroke volume (Philips, Sonos 5500), time intervals at onset and end-ejection, and EF. Stroke volume (SV) was the product of aortic outflow velocity-time integral (apical view) times cross-sectional area. The E/A filling-ratio was assessed using standard methods. M-mode and 2D echocardiograms were obtained in CON-HTN and HF-nlEF patients to assess wall thickness and mass. These data were not available for all young and age-matched normotensive control patients, but none of these patients had documented LVH by ECG, history, or catheterization.

Data Analysis

For invasive studies, Ees was derived from multiple PV loops employing perpendicular regression. This relation can be curvilinear over a full loading range, thus yielding apparent negative volume-intercepts; however, nonlinearity was rarely manifest in the measured range. Noninvasive Ees was estimated by the following
formula: $E_e = (P_s - (E_{es} \times P_r))/E_{es} \times SV$, where $E_{es}$ is the predicted time-amplitude normalized-elastance at the onset of ejection and $P_r$ and $P_s$ are arm-cuff diastolic and systolic pressure, respectively. Diastolic PV relations were obtained from mid to late diastolic points from multiple end-expiratory beats at varying preloads and fit to the following elastic model: Pressure = $P_a + \alpha (e^{\beta a} - 1)$, with chamber stiffness coefficient $\beta$ and pressure-offset $P_a$. Fits were also made to rest beats (before inferior vena cava occlusion) using the full filling period.

Effective arterial elastance ($E_a$) was the ratio of end-systolic pressure ($P_s$) to SV, with ESP measured or estimated noninvasively (CON-HTN) as recently validated. Total arterial compliance was calculated from measured or estimated (transformed radial tonometry) central aortic pressures using a Windkessel model. Isovolumic relaxation was quantified by an exponential model with non-zero asymptote. Systemic vascular resistance was the ratio of pressure (arm-cuff pressure) to cardiac output.

Data in the text and table are presented as mean ± SD. Between-group comparisons were performed by ANOVA, with a Tukey test for multiple comparisons.

**Results**

**Patient Demographics and Hemodynamics**

CON-HTN and HF-nlEF individuals had similar ages and systolic, mean, and pulse pressures (Table). HF-nlEF subjects were predominantly women, had slightly higher resting EF, and greater mean LV wall thicknesses. All groups had similar SV. Heart rate was slightly lower in CON-HTN, which may have reflected the noninvasive setting. Height, weight, and body surface areas were similar between HF-nlEF and the other groups. Concurrent medications included $\beta$-blockers and/or calcium channel blockers, particularly in CON-HTN and HF-nlEF patients. Few subjects had diabetes mellitus.

**Ventricular-Vascular Stiffening in HF-nlEF**

Figure 1A displays representative PV relations from a normotensive control and HF-nlEF patient and shows marked $E_{es}$ and $E_a$ elevation in the latter subject. For the group data, $E_{es}$ was >2-fold higher than normotensive controls and nearly 50% greater than CON-HTN (Figure 1B; *$E_{es}$: HF-nlEF, 4.7 ± 1.5 mm Hg/mL; CON-HTN, 3.3 ± 1.0 mm Hg/mL; young and age-matched normotensives, 2.1 ± 0.88 mm Hg/mL; *P < 0.00001). $E_a$ was 2.6 ± 0.5 mm Hg/mL in HF-nlEF versus 1.9 ± 0.5 mm Hg/mL in other groups (P < 0.0001). $E_{es}$ and $E_a$ directly correlated (Figure 1C). However, coupling ratio ($E_{es}/E_a$) declined in both CON-HTN and HF-nlEF similarly (versus normotensive controls); thus, $E_{es}$ and $E_a$ increase rather than abnormal coupling best identified symptomatic patients.

$E_{es}$ is influenced by systemic vascular resistance, heart rate, and pulsatile load. Systemic vascular resistance did not significantly differ between HF-nlEF and controls (Table), and heart rate was similar in all but CON-HTN patients. To assess pulsatile load more directly, total arterial compliance was determined (Figure 2A). Even after adjusting for mean arterial pressure, SV, and body size (and/or weight), compliance was significantly lower in CON-HTN and HF-nlEF groups versus controls (P < 0.0001) and was reduced more in HF-nlEF than in CON-HTN patients (P < 0.05). Compliance inversely correlated with $E_{es}$ (Figure 2B; regression model including body surface area and SV), with further elevation in $E_{es}$ due to the presence of HF-nlEF (P < 0.05).

**Diastolic Function in HF-nlEF**

HF-nlEF patients had higher EDP than controls (24.3 ± 4.6 versus 12.9 ± 5.5 mm Hg; *P < 0.001) yet similar isovolumic relaxation rates (Figure 3A). The $E/A$ ratio was lower in both CON-HTN and HF-nlEF subjects versus normotensive controls and so did not distinguish between symptomatic and asymptomatic patients (Figure 3A). However, end-diastolic pressure-volume relations (EDPVR) were abnormal in HF-nlEF patients by being shifted significantly upward in both early and late diastole. Figure 3B shows data from a HF-nlEF subject and displays both the resting curve and data obtained from multiple beats at varying preload after internal vena cava occlusion.
cava obstruction. Rest data were generally shifted above that measured after right ventricular unloading, particularly during initial filling. From these data, both pressure offset (Po; 9.3 ± 5.2 versus 0.52 ± 0.6 mm Hg; \(P<0.0001\)) and chamber stiffness (\(\beta\); 0.06 ± 0.03 versus 0.036 ± 0.2; \(P<0.02\)) were higher in HF-nlEF than controls (Figure 3C). The latter correlated with LV mass (\(P<0.05\)). Po, derived from the multibeat analysis was less, but still greater in HF-nlEF than controls (5.4 ± 5.6 versus 0.61 ± 4.0 mm Hg; \(P<0.002\)). However, \(\beta\) from these data no longer differed between groups (0.03 ± 0.01 versus 0.029 ± 0.01 mL⁻¹; \(P=0.8\)).

### Coupling Ventricular/Arterial Stiffening and Diastolic Function

Combined ventricular-arterial stiffening augments systolic pressures at higher loads\(^{13}\) and could thus adversely impact diastolic relaxation and pressure.\(^{14}\) Figure 4 shows PV data from example HF-nlEF patients before and during hand grip exercise, revealing a hypertensive response concordant with the high basal Ees, and elevated EDP during stress. On average, ESP rose to 200.5 ± 12.3 mm Hg, EDP to 32.3 ± 8.6 mm Hg, and relaxation time to 85.7 ± 23.1 ms (all \(P<0.05\) versus baseline). Unlike baseline, relaxation during exercise was significantly longer in HF-nlEF patients than controls (58.9 ± 21 ms; \(P<0.05\)); the latter group also generated a lower ESP (169 ± 24 mm Hg; \(P<0.01\) versus HF-nlEF). Analysis of only handgrip exercise (used in the majority of subjects) yielded similar disparities (ie, ESP=202 ± 1 mm Hg and tau=95.4 ± 18.2 ms in HF-nlEF patients versus 166 ± 24 mm Hg and 55.6 ± 20.1 ms in controls; \(P<0.01\) for both versus HF-nlEF).

### Discussion

Heart failure with preserved systolic function is fairly common, yet its pathophysiology remains uncertain. Most studies have focused on diastolic abnormalities, and the term diastolic heart failure is often used synonymously. Although diastolic parameters are often abnormal,\(^{8}\) they are not necessarily the sole or dominant factors defining dysfunction, nor do they necessarily guarantee clinical heart failure\(^{22}\) or exertional dyspnea.\(^{10}\) Furthermore, having a preserved EF does not automatically imply that systolic function is normal, as demonstrated by the increased systolic stiffening found in
HF-nIEF patients in the present investigation. Recent studies have begun exploring other contributors, such as arterial stiffening, although the role of hypertension per se in this change has remained unclear. The present study provides evidence supporting both vascular and ventricular-systolic stiffening in these patients and demonstrates that both abnormalities cannot be simply ascribed to age, body size, SV, or arterial pressure differences. These findings may better explain common features of HF-nIEF and help broaden its pathophysiological and therapeutic focus.

Pathophysiology of Systolic-Ventricular and Arterial Stiffening

Combined systolic-ventricular and arterial stiffening can influence cardiovascular function in several ways. First, a high basal $E_{es}$ blunts contractile reserve, because further increase coupled to positive inotropy is limited and has only modest effects on net ejection. Whether a high basal $E_{es}$ itself reflects intrinsic contractility is less clear, because structural changes from hypertrophy or fibrosis can also increase $E_{es}$. Second, high $E_{es}$ and $E_{a}$ augment systolic pressure sensitivity to cardiac loading, exacerbating hypertensive responses during exertion. Verapamil lowers both parameters, thus enhancing aerobic exercise capacity in the elderly. Enhanced sensitivity of blood pressure to circulating volume and diuretics is common in HF-nIEF patients and may trigger rapid-onset pulmonary edema. Although ascribed to low LV diastolic compliance, similar blood pressure sensitivity is not observed in systolic-depression with elevated EDP. Rather, combined ventricular-systolic/arterial stiffening more directly predicts enhanced pressure-load dependence, perhaps favoring blood redistribution into more compliant pulmonary veins.

Another consequence of ventricular-arterial stiffening may be increased cardiac energy costs to provide blood flow. Arterial stiffening raises myocardial oxygen consumption for a given SV, and ventricular systolic stiffening amplifies this effect. As shown by model analysis (Figure 5), higher $E_{es}$ and/or $E_{a}$ increase the cardiac energy cost to deliver a given increase in SV. On the basis of the present data, this energy cost is predicted to be >50% higher HF-nIEF versus controls and might limit reserve in those with concomitant heart or coronary artery disease.

Finally, increased ventricular-arterial stiffening and the consequent rise in systolic pressure during stress can worsen diastolic function, as demonstrated by the exercise data. Cardiac relaxation is delayed by elevated systolic pressure and can translate into increased EDP. Elevated $E_{es}$ and $E_{a}$ in HF-nIEF patients likely exacerbate hypertensive stress responses (Figure 4), delaying relaxation, limiting filling, and raising diastolic pressures.
Diastolic Dysfunction in HF-nlEF
The majority of evidence supporting diastolic dysfunction in HF-nlEF is based on noninvasive analysis, revealing relaxation delay, increased velocity of E-wave deceleration, and an E:A velocity ratio < 1.0.8,27 As in the present study, the latter is often found in asymptomatic elderly and/or hypertensive individuals22 and is thus less specific. Invasive data are limited, but recent studies have shown a high prevalence of EDP elevation > 16 mm Hg (92%) and relaxation delay (79%).8 HF-nlEF patients in the present study also had elevated EDP, although relaxation decay was more variable. The latter may relate to a lower incidence of LVH and to relaxation analysis incorporating a non-zero pressure decay asymptote. Elevation of EDPVR, and thus P_o, increases the derived relaxation constant when zero-pressure decay is assumed.19
Far less is known about the diastolic PV curve in HF-nlEF, and although it is assumed to be steeper,8 there are very few data to confirm this. Kitzman et al.28 found that exercise intolerance in HF-nlEF patients was associated with higher EDP at a similar end-diastolic volume, suggesting failure of the Frank-Starling mechanism. Similar changes were observed in the present study (Figure 4). Yet, such EDPVR shifts are more often due to higher extrinsic forces coupling right-left heart pressure19 than to intrinsic stiffening. The present study assessed EDPVR from both rest-data and multiple cycles measured after right heart/pericardial unloading. At rest (condition that EDP is usually measured), the EDPVR was shifted upward (increased P_o), with a higher β stiffness coefficient. Elevation of the early filling phase of this relation may reflect loading influences on relaxation,14 but may also be ascribed to higher left atrial pressures that determine the pressure at mitral valve opening (ie, onset of filling). Both P_o and β declined when derived from the data measured with right ventricular unloading, with no residual difference in β between HF-nlEF and controls; this highlights the importance of loading conditions to the resting EDPVR. One potential source of such loading in HF-nlEF is enlargement of epicardial volumes from wall thickening with normal cavity volumes.29 Right heart pressures were not available to assess this offset directly, but the decline in P_o between rest and internal vena cava occlusion data supports this mechanism.30 Clearly, diastolic dysfunction was present in HF-nlEF patients as well, but the precise nature of EDPVR changes were somewhat different to that generally held, and suggested a more prominent role of loading.

Study Comparisons and Limitations
There are some differences between the present study and recently reported data that deserve comment. LVH was documented in 60% of the HF-nlEF subjects, whereas it was required for entry in the study of Zile et al.,8 and this may explain some disparities. However, nearly a third of the asymptomatic CON-HTN subjects also met LVH criteria. Thus, although common, LVH is not required for HF-nlEF. In addition, HF-nlEF patients were somewhat younger in our study than in other reports,1,2,3,1 whereas they were very similar to populations in others.8

The present study has several limitations. A methodological one is that CON-HTN subjects were not studied invasively. These patients had no primary indication for catheterization, and hypertensive individuals of advanced age with normal hearts and coronary arteries are rarely referred to our invasive laboratory. Although this necessitated noninvasive analysis, these methods have been validated against invasive measures, showing excellent correlation without systematic bias.27 Mean arterial pressure was estimated from systolic/diastolic cuff data in CON-HTN. However, comparisons of this approach to actual waveform means (invasive studies) yielded a strong correlation (P < 10^-5; r = 0.94; slope = 0.99). We could not rule out effects of chronic medications on measured systolic and diastolic function. However, if anything, HF-nlEF patients were more likely treated with one or both of a β-adrenergic or Ca^2+ channel blocker, both of which reduce E_a and may lower E_e as well.24 Estimation of chamber stiffness from diastolic curves has limitations given that the equilibrium volume cannot be precisely determined in the intact heart. Finally, the control groups did not fully reflect features observed in the HF-nlEF patients, for example, the female sex bias, and this could have contributed to the findings. Although E_e and E_a are reportedly higher in women (of similar age to subjects in the present study),32 this difference is far less than observed in the HF-nlEF patients (ie, E_e of 2.65 versus 1.96). Importantly, higher E_e and E_a in women occurred with smaller heart sizes and SVs,32 whereas neither differed among groups in the present study.

Conclusions
HF-nlEF is not solely a diastolic disease but is also characterized by systolic-ventricular and arterial stiffening and, thus, adverse coupling between the systems. This may more directly explain the systemic pressure lability and diuretic sensitivity that is commonly observed. By limiting mechanisms of cardiovascular reserve, exacerbating diastolic abnormalities, and potentially raising cardiac energy demand, combined stiffening may play an important pathophysiological role in this disorder. To date, no specific therapies have been proven to benefit this form of heart failure, although several trials are now underway to address this. Expanding the conceptual view of HF-nlEF to include abnormal cardiac-arterial coupling and testing the impact of reducing heart/arterial stiffening in these patients should further help in the search for such therapies.

References


