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Effects of Vasodilation in Heart Failure With Preserved or Reduced Ejection Fraction

Implications of Distinct Pathophysiologies on Response to Therapy

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Objectives The purpose of this study was to compare hemodynamic responses to vasodilator therapy in patients with heart failure (HF) and preserved ejection fraction (HFpEF) versus HF and reduced ejection fraction (HFrEF).

Background There is no proven therapy for HFpEF. In the absence of data, medicines with established benefit in HFrEF such as vasodilators are frequently prescribed for HFpEF.

Methods We compared baseline hemodynamics and acute responses to vasodilation with intravenous sodium nitroprusside in patients with HFrEF (n = 174) and HFpEF (n = 83), determined invasively by cardiac catheterization.

Results Baseline blood pressure, stroke volume, and cardiac output were greater in HFpEF than HFrEF, while pulmonary artery mean and pulmonary wedge pressures were similar. Left ventricular filling pressures were reduced to a similar extent in each group with nitroprusside, but the drop in systemic arterial pressure was 2.6-fold greater in HFpEF ($p < 0.0001$), and improvements in stroke volume and cardiac output were each ~60% lower in HFpEF compared to HFrEF ($p < 0.0001$). Despite similarly elevated filling pressures, HFpEF patients were fourfold more likely than HFrEF to experience a reduction in stroke volume with nitroprusside ($p < 0.0001$), suggesting greater vulnerability to preload reduction. Pulmonary artery systolic pressure dropped more in HFpEF than in HFrEF despite similar reduction in pulmonary mean pressure and resistance, suggesting higher right ventricular systolic elastance in HFpEF.

Conclusions As compared to patients with HFrEF, patients with HFpEF experience greater blood pressure reduction, less enhancement in cardiac output, and greater likelihood of stroke volume drop with vasodilators. These findings emphasize fundamental differences in the 2 HF phenotypes and suggest that more pathophysiologically targeted therapies are needed for HFpEF. (J Am Coll Cardiol 2012;59:442–51) © 2012 by the American College of Cardiology Foundation

Approximately one-half of patients with heart failure (HF) have preserved ejection fraction (HFpEF) and the remainder have heart failure with reduced ejection fraction (HFrEF) (1). Clinical presentation is similar in both forms of HF, and because abnormalities in ventricular and vascular function are common to each, it has been proposed that HFpEF and HFrEF are part of the same "HF continuum" (2). However, therapies with unequivocal benefit in HFrEF have failed to show efficacy in HFpEF (3–5), suggesting important pathophysiologic differences. In the absence of proven treatments for HFpEF, it is important to understand potential differences in response to empiric HF therapies, and appreciation of unique pathophysiology in the 2 types of HF may better inform selection of interventions to be tested in future trials.

Vasodilators are a cornerstone in the management of both decompensated and chronic HFrEF (3–7). Favorable acute hemodynamic effects of vasodilation in HFrEF are due in large part to enhanced afterload sensitivity of the dilated, failing ventricle (7–9). Although systolic function is not completely normal in HFpEF, both systolic and diastolic ventricular vascular stiffness are typically elevated (10,11), Theoretical and clinical data from small studies suggest that this combined ventricular-arterial stiffening may promote exaggerated blood pressure response to changes in ventricular loading in HFpEF, including hypertensive crisis with vasoconstriction, or hypotension with overly aggressive vasodilation (10,12).

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We sought to compare the acute hemodynamic effects of vasodilation with nitroprusside in patients with HFpEF and HFrEF. We hypothesized that hemodynamic changes with vasodilation are fundamentally different in the 2 HF populations—with greater systemic arterial pressure drop and

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less augmentation of stroke volume in HFpEF as compared to HFrEF.

Methods

Study population. We examined consecutive patients with HF referred to the Mayo Clinic cardiac catheterization laboratory between October 2002 and July 2009 for right heart catheterization (with or without left heart catheterization) who underwent acute vasodilator challenge with intravenous sodium nitroprusside. Nitroprusside is routinely administered in our laboratory when pulmonary wedge pressure is elevated to assess reversibility. Patients with primary left-sided valvular heart disease, cardiac transplantation, on inotrope or pressor therapy, with complex congenital disease or shock were excluded. The study was approved by the Mayo Clinic institutional review board.

Catheterization protocol. Patients were studied receiving chronic medications in the fasted state after minimal sedation in the supine position. Standard right heart catheterization was performed through the internal jugular or femoral vein. Left heart catheterization was performed by the retrograde transaortic approach from the radial or femoral artery, as described previously (13), in a subset of patients (n = 89). All measurements were performed at end-expiration off line by 1 investigator (S.S.) from electronically stored continuous recordings of pressure tracings. Systemic arterial blood pressure (BP) was measured invasively (n = 217) or by cuff sphygmomanometry (n = 40). Cardiac output was determined by the Fick method or by thermodilution. Stroke volume (SV) was determined by cardiac output divided by heart rate.

Nitroprusside infusion. After baseline hemodynamic data were acquired, sodium nitroprusside was administered at incremental doses starting at 0.25 to 0.5 μg/kg/min, titrated to: 1) normalization in pulmonary wedge pressure; 2) reduction in systolic BP to <90 mm Hg; or 3) patient intolerance (e.g., lightheadedness). Hemodynamic measurements were then repeated.

Case definitions. Clinical data were obtained from detailed chart review. Echocardiographic data was abstracted from clinically obtained studies performed before catheterization. HFpEF was defined by cardiologist adjudicated HF diagnosis (Framingham criteria), EF >50%, the absence of significant valvular disease (more than moderate left-sided regurgitation or any stenosis), and after exclusion of patients with constrictive pericarditis, and infiltrative, restrictive, or hypertrophic cardiomyopathies. HFrEF was defined employing the same criteria, with EF <50%. Patients with HFrEF and functional mitral regurgitation were not excluded, provided that primary mitral valve pathology was absent.

Hemodynamic definitions. LV end-systolic and end-diastolic volumes were determined from the Teicholz method based upon echocardiography. Left ventricular preload was defined by end-diastolic volume (12). LV end-systolic volume changes during nitroprusside infusion were estimated by the difference in echocardiographic end-diastolic volume and directly measured SV. LV end-systolic pressure was taken as 0.9*systolic BP. The LV end-systolic elastance (Ees) was estimated by the ratio of end-systolic pressure to end-systolic volume. Systemic arterial afterload was assessed by effective arterial elastance (Ea), defined as the ratio of end-systolic pressure to SV (12). Ventricular-arterial coupling was assessed by the ratio of Ea/Ees (12). Pulsatile load, referring to the nonresistive, oscillatory components of arterial afterload, was assessed by systemic arterial pulse pressure and compliance (SV divided by pulse pressure) (14). Pulmonary vascular resistance was determined using standard formula (13).

Abbreviations and Acronyms

- **BP** = blood pressure
- **Ea** = effective arterial elastance
- **Ees** = end-systolic elastance
- **HF** = heart failure
- **HFpEF** = heart failure with preserved ejection fraction
- **HFrEF** = heart failure with reduced ejection fraction
- **LV** = left ventricular
- **RV** = right ventricle
- **SV** = stroke volume

Statistical analysis. Data are reported as mean ± SD or median (25th, 75th interquartile range). Between-group differences were compared by *t* test, Wilcoxon rank-sum test, or chi-square. Bivariate regression (Pearson coefficient) was used to examine correlations between continuous measures. Multivariable linear regression analysis was used to adjust for relevant baseline group differences, in which the dependent variable was the normally distributed continuous or categorical outcome variable of interest, and factors entered into the model included age, sex, body mass, group (dummy variable), and relevant interaction terms. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by quantile plots, and no major violations were observed.

Results

Subject characteristics. Between October 2002 and July 2009, 449 patients received nitroprusside infusion during invasive hemodynamic study. From this population, 174 patients were identified with HFrEF and 83 with HFpEF. (Diagnoses for excluded patients are provided in the Online Appendix.) Patients with HFpEF were older, more likely to be female and hypertensive, and had larger body mass index compared with HFrEF (Table 1). Patients with HFrEF were more likely to be treated with beta-blockers, digoxin, and inhibitors of the angiotensin-aldosterone axis, and less likely to be treated with calcium-channel blockers compared with HFpEF patients. Most patients were receiving diuretics. Natriuretic peptide and serum hemoglobin levels were higher in HFrEF patients. Cardiomegaly on chest film was more common in HFrEF patients.

Echocardiography was performed a median of 6 days (interquartile range: 2 to 28 days) before catheterization,

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Table 1 Baseline Characteristics

	HFrEF (n = 174)	HFpEF (n = 83)	p Value
Age, yrs	56 ± 12	69 ± 9	<0.0001
Female	25	71	<0.0001
Body mass index, kg/m^2	29.5 ± 5.8	33.2 ± 8.3	<0.0001
Body surface area, m^2	2.07 ± 0.25	2.05 ± 0.30	0.60
Comorbidities			
Hypertension	48	66	0.02
Diabetes mellitus	44	45	0.90
Coronary disease	69	61	0.40
COPD	17	18	0.90
Medications			
Beta-blockers	90	78	0.002
ACEI or ARB	88	76	0.02
Diuretics	95	89	0.10
Aldosterone antagonists	48	16	<0.0001
Digoxin	58	20	<0.0001
Calcium antagonists	8	41	<0.0001
Laboratory values			
Sodium, mmol/l	139 (137–141)	141 (138–142)	<0.0001
Hemoglobin, g/dl	13.0 ± 1.9	12.1 ± 1.7	0.001
GFR, ml/min/1.73 m^2	65 (45–80)	57 (47–69)	0.10
NT-proBNP, pg/ml	3,913 (2,177–8,160)	1,360 (781–3,716)	0.002
BNP, pg/ml	751 (352–1,520)	371 (206–597)	0.0001
Cardiomegaly on chest film	73	56	0.01
Echocardiography			
LV septum, mm	10 (9–11)	10 (10–12)	<0.0001
LV diastolic dimension, mm	68 ± 11	48 ± 5	<0.0001
LV end-diastolic volume, ml	246 ± 90	108 ± 28	<0.0001
LV mass, g	311 ± 105	198 ± 56	<0.0001
LV mass/end-diastolic volume	1.32 ± 0.38	1.91 ± 0.57	<0.0001
Left atrial volume, ml/m^2	58 ± 19	49 ± 22	<0.0001
LV ejection fraction, %	22 ± 9	63 ± 6	<0.0001
Grade 3 or 4 mitral regurgitation, %	27	0	<0.0001
Severe tricuspid regurgitation, %	19	15	0.50
E/A ratio	2.5 (1.7–3.3)	1.3 (1.1–2.1)	<0.0001
Tissue Doppler E', cm/s	4.0 (3.0–5.0)	6.0 (4.0–7.0)	<0.0001
E/e' ratio	22 (17–32)	18 (14–27)	0.007
Deceleration time, ms	139 ± 34	179 ± 39	<0.0001
RV dysfunction,* %	54	18	<0.0001

Values are mean ± SD, %, or median (25th to 75th interquartile range). *Refers to qualitative impression based upon echocardiography, as abstracted from the clinical records.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; E/A = transmitral early to late filling velocity ratio; E/e' = early diastolic transmitral flow to tissue velocity ratio; GFR = glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide; RV = right ventricular.

with no difference between groups in the interval (p = 0.60). LV chamber dimension, mass, volumes, and left atrial size were greater in HFrEF, whereas wall thickness and the ratio of wall thickness to chamber volume were higher in HFpEF (Table 1). Patients with HFrEF more commonly displayed qualitative right ventricular systolic dysfunction and had more severe LV diastolic dysfunction based upon Doppler echocardiography, compared with HFpEF.

Baseline hemodynamics. At rest, right atrial, mean pulmonary artery, and pulmonary wedge pressures were similar in HFpEF and HFrEF, although LV end-diastolic pressures were somewhat higher in HFrEF (Table 2). Patients with HFpEF had higher BP, pulmonary artery systolic pressure, cardiac output, and SV compared with HFrEF, while heart rate and pulmonary vascular resistance were similar in both groups. Pulmonary artery saturations were lower in HFrEF compared with HFpEF, yet 75% of HFpEF patients displayed saturations below the normal range (<68%), consistent with inadequate perfusion relative to metabolic needs.

The pulsatile contribution to systemic arterial pressure was greater in HFpEF, evidenced by higher pulse pressure, lower arterial compliance, and greater systolic BP for any arterial elastance (Ea) (Fig. 1). Ventricular-arterial coupling

Table 2 Baseline Hemodynamics

	HFrEF (n = 174)	HFpEF (n = 83)	p Value
Peripheral hemodynamics			
Heart rate, beats/min	70 (62–81)	70 (60–76)	0.20
Systolic BP, mm Hg	113 (100–127)	166 (144–180)	<0.0001
Mean BP, mm Hg	80 (74–92)	104 (93–118)	<0.0001
Systemic arterial saturation, %	93 (90–96)	94 (90–96)	0.80
Central hemodynamics			
Right atrial pressure, mm Hg	14 ± 6	14 ± 6	0.80
Mean PA pressure, mm Hg	40 ± 9	41 ± 10	0.50
PA systolic pressure, mm Hg	59 ± 14	64 ± 18	0.02
PCWP, mm Hg	25 ± 6	22 ± 6	0.30
LV end-diastolic pressure, mm Hg	26 ± 6	22 ± 6	0.008
Flow and resistance data			
Cardiac output, l/min	4.0 (3.4–4.8)	4.7 (4.1–6.0)	<0.0001
SV, ml	58 (44–71)	73 (56–85)	<0.0001
Pulmonary artery saturation, %	55 (50–62)	61 (57–67)	<0.0001
PVR, Woods units	3.3 (2.4–4.6)	3.3 (2.0–5.0)	0.80
Arterial-ventricular coupling			
Ees, mm Hg/ml	0.54 (0.40–0.85)	3.7 (3.0–4.7)	<0.0001
Ea, mm Hg/ml	1.7 (1.5–2.4)	2.0 (1.6–2.8)	0.03
Coupling ratio, Ea/Ees	3.3 (2.1–4.8)	0.58 (0.40–0.72)	<0.0001

Values are mean ± SD or median (25th to 75th interquartile range).
BP = blood pressure; Ea = effective arterial elastance; Ees = left ventricular end-systolic elastance; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SV = stroke volume; other abbreviations as in Table 1.

was more deranged in HFrEF: LV Ees was nearly an order of magnitude lower compared with HFpEF (Table 2), whereas baseline Ea was somewhat higher in HFpEF. The coupling ratio (Ea/Ees) was fivefold higher in HFrEF compared with HFpEF, consistent with afterload mismatch. All group differences persisted after adjusting for age, sex, and body mass index.

Hemodynamic responses with nitroprusside. There was no difference in nitroprusside dose administered between the groups (Table 3). Cardiac output was remeasured during

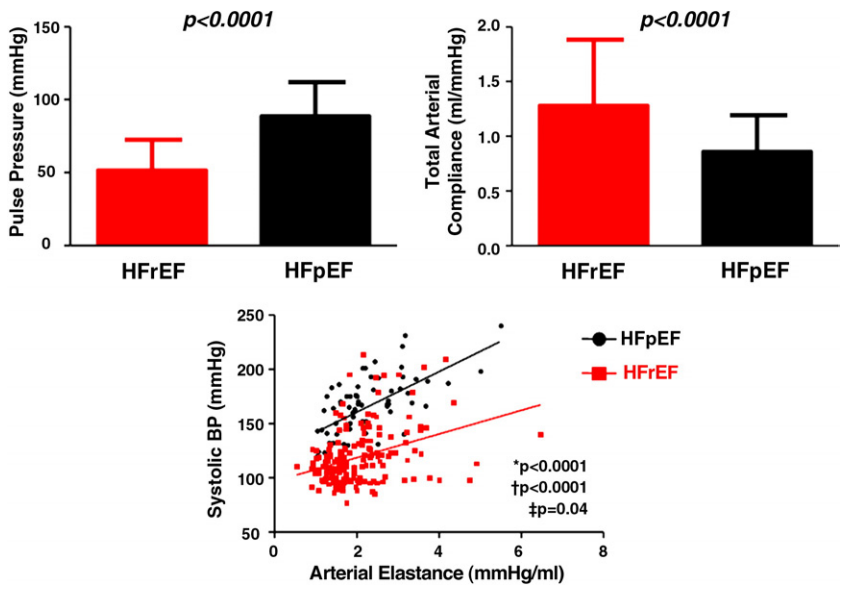

Figure 1 Pulsatile Arterial Loading in HFpEF and HFrEF

Pulsatile afterload was greater in heart failure with preserved ejection fraction (HFpEF) **(black)** compared with heart failure with reduced ejection fraction (HFrEF) **(red)**, with higher pulse pressure, lower arterial compliance, and higher systolic arterial pressure for a given arterial elastance. The p values are shown for *bivariate, †group, and ‡interaction term comparisons. BP = blood pressure.

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Table 3 Hemodynamic Changes With Nitroprusside

	HFrEF (n = 174)	HFpEF (n = 83)	p Value
Nitroprusside dose, μg/kg/min	1.5 (1–3)	2 (1–2)	0.50
Peripheral changes			
Δ Heart rate, beats/min	+2 ± 9	+4 ± 9	0.15
Δ Systolic BP, mm Hg	−22 (−11 to −36)	−51 (−28 to −71)	<0.0001
Δ Mean BP, mm Hg	−18 (−10 to −27)	−30 (−19 to −42)	<0.0001
Central changes			
Δ Mean PA pressure, mm Hg	−12 ± 8	−11 ± 8	0.70
Δ PA systolic pressure, mm Hg	−15 ± 11	−19 ± 13	0.02
Δ PCWP, mm Hg	−9 ± 6	−9 ± 6	0.70
Δ LV end-diastolic pressure, mm Hg	−8 ± 5	−9 ± 6	0.90
Flow and resistance changes			
Δ Cardiac output, l/min	+1.9 ± 1.4	+0.8 ± 1.4	<0.0001
Δ SV, ml	+23 ± 20	+8 ± 21	<0.0001
Δ PVR, Woods units	−1.4 (−0.7 to −2.4)	−1.1 (−0.1 to −2.0)	0.09
Δ Ea, mm Hg/ml	−0.8 (−0.4 to −1.3)	−0.6 (−0.5 to −1.2)	0.40

Values are mean ± SD or median (25th to 75th interquartile range).
Abbreviations as in Tables 1 and 2.

nitroprusside in 157 HFrEF patients and 51 HFpEF patients, and all subjects had paired measures of pressure data. There were no differences in baseline characteristics between patients who did and did not have cardiac output remeasured during nitroprusside (Online Appendix). Despite similar reductions in systemic afterload (Ea) with nitroprusside in both groups, patients with HFpEF experienced ~2.5- and ~1.7-fold greater drops in systolic and mean arterial BP compared with HFrEF (Fig. 2, Table 3). Conversely, patients with HFrEF displayed twofold to 3-fold greater increases in SV and cardiac output compared with HFpEF. The proportional increase in SV (relative to baseline) with nitroprusside was fourfold greater in HFrEF than HFpEF (+49 ± 50% vs. +13 ± 31%, p < 0.0001). Changes in heart rate and LV filling pressures with nitroprusside were similar in HFrEF and HFpEF (Fig. 2, Table 3). Each of these differences persisted after adjusting for age, sex, body mass index, and nitroprusside dose.

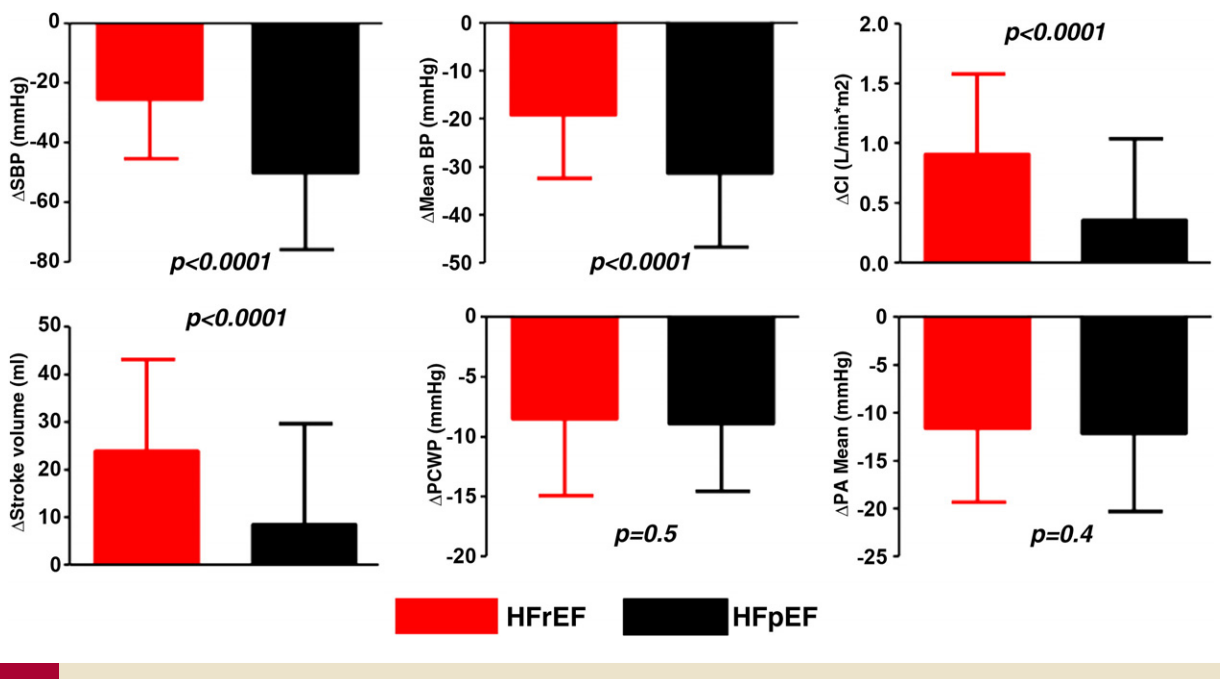

Figure 2 Peripheral and Central Hemodynamic Changes With Nitroprusside

Nitroprusside caused greater blood pressure (BP) reduction in heart failure with preserved ejection fraction (HFpEF) **(black)** compared with heart failure with reduced ejection fraction (HFrEF) **(red),** whereas augmentation in stroke volume (SV) and cardiac output were greater in HFrEF compared with HFpEF. PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

The HFrEF patients with significant (grade 3 to 4) mitral regurgitation tended to show greater hemodynamic improvements compared to HFrEF patients without mitral regurgitation, but after restricting the analysis to HFrEF without significant mitral regurgitation, each of the HFpEF-HFrEF group comparisons remained highly significant (Online Appendix). Group differences in stroke volume, cardiac output, and blood pressure persisted after recategorizing HFpEF as patients with EF >45% and EF >40%.

Figure 3A shows the distributions of SV change with nitroprusside in HFrEF and HFpEF. Despite the predominant arterial vasodilator properties of nitroprusside (6) and the presence of elevated LV filling pressures, SV actually decreased in 35% of HFpEF patients with nitroprusside, compared with only 9% of HFrEF patients ($p < 0.0001$). Subgroup analysis revealed that baseline pulmonary capillary wedge pressure was lower and the increase in heart rate greater with nitroprusside among patients with a drop in SV compared to patients with enhanced SV, but LV filling pressures were elevated in both groups (Online Appendix). Importantly, observed disparities in BP, SV, and cardiac output response to nitroprusside in HFpEF and HFrEF persisted after excluding patients with SV reduction or with baseline pulmonary wedge pressures below 20 or 25 mm Hg (Online Appendix).

Determinants of the nitroprusside response. The reduction in BP with nitroprusside correlated with the decrease in arterial afterload (Ea) in all patients ($p < 0.0001$), but for any drop in Ea, the reduction in systolic BP was steeper in HFpEF compared with HFrEF (group $p < 0.0001$; interaction term $p = 0.003$) (Fig. 3B). These differences persisted after adjusting for age, sex, and body mass index. Changes in pulmonary wedge pressure with nitroprusside were not related to changes in BP, SV, heart rate, cardiac output, or Ea. Enhancement in SV as a function of LV filling pressure was greater in HFrEF than HFpEF (Fig. 3C).

Changes in LV end-systolic pressure and estimated end-systolic volume with nitroprusside are displayed graphically in Figure 4, plotting median baseline Ees estimates (solid lines), end-diastolic volumes from echocardiography, and observed reductions in Ea (dashed lines). Assuming that Ees and end-diastolic volume did not change on average with nitroprusside, observed changes in end-systolic pressure-volume coordinates (diamonds) fall very close to

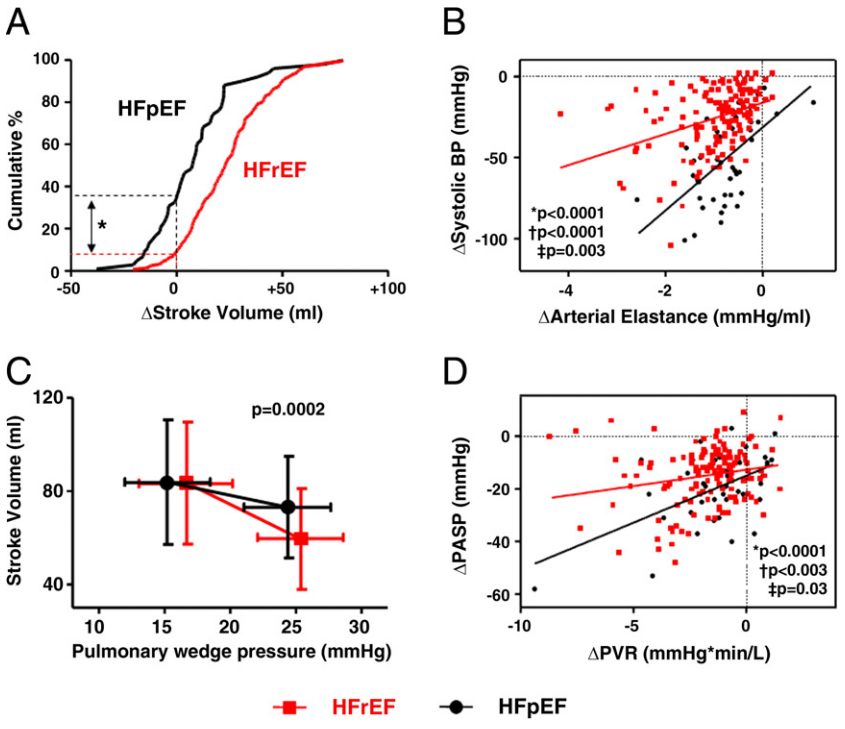

Figure 3 Pressure-Flow Changes With Load Alteration

(A) Cumulative distribution plot shows attenuated enhancement in stroke volume (SV) in heart failure with preserved ejection fraction (HFpEF) **(black)** compared with heart failure with reduced ejection fraction (HFrEF) **(red)**, as 35% of HFpEF patients displayed a reduction in SV with nitroprusside compared with 9% of HFrEF (*$p < 0.0001$) **(dashed lines)**. **(B)** Drop in systemic arterial blood pressure (BP) was accentuated for any degree of vasodilation (Ea reduction) in HFpEF compared with HFrEF. **(C)** Increase in SV as a function of left ventricular filling pressure with nitroprusside was greater in HFrEF. **(D)** Reduction in pulmonary artery systolic pressure (PASP) with vasodilation was greater in HFpEF compared to HFrEF. The p values in B and D reflect *bivariate, †group, and ‡interaction term comparisons. See text for details.

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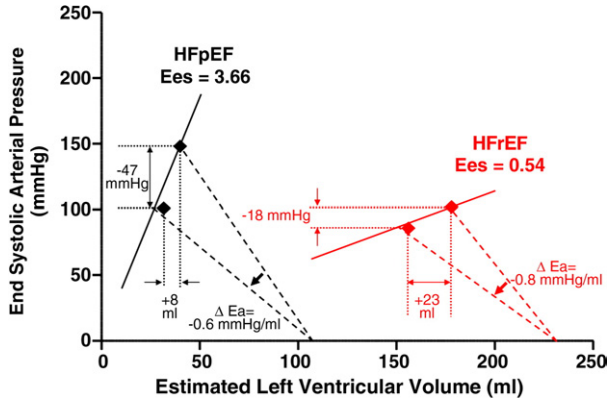

Figure 4 **Observed and Predicted End-Systolic Pressure-Volume Changes With Nitroprusside**

Observed changes in estimated end-systolic pressure-volume coordinates **(diamonds)** in heart failure with preserved ejection fraction (HFpEF) **(black)** compared with heart failure with reduced ejection fraction (HFrEF) **(red)** with reduction in arterial elastance (Ea) **(dashed lines)** were very similar to those predicted based on resting left ventricular end-systolic elastance (Ees) **(straight lines)** and the observed changes in Ea. See text for details.

values predicted by the estimated baseline end systolic pressure-volume relationships (Fig. 4).

Right-sided ventricular-arterial coupling. Despite similar mean pressures, pulmonary artery systolic pressure was higher in HFpEF than in HFrEF (Table 2), even after adjusting for pulmonary wedge pressure, pulmonary vascular resistance, and SV. With nitroprusside, pulmonary artery systolic pressure decreased more in HFpEF than in HFrEF despite similar changes in pulmonary wedge pressure and pulmonary arteriolar resistance (Table 3). After adjusting for changes in pulmonary wedge pressure and pulmonary vascular resistance, the drop in pulmonary arterial systolic pressure was greater in HFpEF than in HFrEF (Fig. 3D), suggesting higher right ventricular Ees in HFpEF and greater right ventricular afterload mismatch in HFrEF.

Discussion

We compared hemodynamics at rest and during nitroprusside infusion in a large cohort of well-characterized patients with HF and preserved or reduced ejection fraction. In the left-sided circulation, we observed greater pulsatile arterial loading in HFpEF and greater LV-arterial mismatch in HFrEF, as previously demonstrated. We show that these alterations in ventricular-arterial properties in HFpEF and HFrEF are associated with fundamental differences in the response to vasodilation. Patients with HFpEF had more exaggerated drops in BP and less enhancement in SV and cardiac output compared with HFrEF. LV filling pressures were similarly elevated in patients with HFrEF and HFpEF at baseline. With nitroprusside, filling pressures dropped to similar extent in both forms of HF, yet patients with HFpEF were more likely to experience a reduction in SV, suggesting greater vulnerability to venodilator effects and excessive drop in preload. In the right ventricular-pulmonary arterial circulation, we also observed more exaggerated drops in systolic arterial pressure despite similar reduction in pulmonary venous pressures. These findings emphasize important mechanistic differences in the 2 distinct HF phenotypes and raise questions regarding the empiric use of vasodilator-based treatment approaches in the absence of established indications in patients with HFpEF.

Surprisingly few studies have compared hemodynamics in HFpEF and HFrEF, and none have contrasted responses to clinical intervention. van Heerebeek et al. (15) examined LV properties in 22 patients with HFpEF and 22 patients with HFrEF. As in the current study, LV filling pressures at rest were similarly elevated in HFpEF and HFrEF, leading the authors to suggest that hemodynamics alone do not distinguish these HF phenotypes. Although the current data confirm similarities in filling pressures at baseline, they highlight important, fundamental differences in arterial pressure and flow responses with vasodilation in HFpEF and HFrEF in both the left- and right-sided circulations. These findings may have important implications for the care of patients with HFpEF.

Ventricular-arterial interaction in HF. Changes in BP and SV with alteration in ventricular loading conditions are predictable based upon concepts of ventricular-arterial coupling (8,9,12,16). BP decreases while the SV increases with vasodilation, and the extent of change in each is dictated by slope and intercept of the end-systolic pressure volume relationship, termed end-systolic elastance (Ees) (Fig. 4). While elevated arterial afterload (Ea) is common to both forms of HF, the 2 entities differ dramatically in the "active" stiffness (contractility) developed by the heart at end systole, or Ees (8,17). In HFpEF, Ees is elevated (10), despite mild abnormalities in myocardial and chamber contractility (11), likely because passive components of stiffness are elevated (15). In an elegant study, Kawaguchi et al. (10) demonstrated that elevated Ees in HFpEF leads to an exaggerated hypertensive response to isometric handgrip, providing mechanistic insight into to the hypertensive pulmonary edema commonly observed in these patients (18). We show for the first time in a large series of HFpEF patients the converse is also true: with acute decreases in afterload, there are also more dramatic drops in BP. The average changes in pressure and volume were strikingly similar to those predicted based upon median estimated end-systolic pressure-volume relationships in HFpEF patients (Fig. 4).

In contrast, the shallow end-systolic pressure volume relationship in HFrEF (low Ees) (Fig. 4) predicts the opposite: lesser drop in BP and higher gain in SV with Ea reduction. This phenomenon allows HFrEF patients to tolerate very high doses of vasodilators without hemodynamic embarrassment, as previously described (6–8). In healthy humans, Ees and Ea are closely matched to optimize stroke work and efficiency, with Ea/Ees ratios of 0.5 to

1.0 (9,11,16). In HFrEF, Ea/Ees is elevated because contractility (Ees) is depressed, creating afterload mismatch, such that the failing heart is operating farther from optimal efficiency (16,17). Enhanced coupling in HFrEF is best achieved pharmacologically through vasodilation rather than augmentation of Ees, because of the increased myocardial oxygen demand and toxicity associated with inotropes (12).

In the HFpEF subjects in this study and previous reports (10), Ea/Ees was ~0.5 at baseline, indicating that the ventricular-arterial system was already operating at near maximum efficiency (9,16). Therefore, there was less to be gained from vasodilation from a mechanical pump perspective. This observation, combined with the potentially greater risk of hypotension or depression of SV, suggests that vasodilator-based approaches may not be as broadly applicable to HFpEF as they are to HFrEF. An important exception is the HFpEF patient with uncontrolled hypertension or hypertensive pulmonary edema, wherein vasodilator therapy is very effective to control BP and relieve symptoms of HF (18).

In addition to ventricular stiffening, vascular stiffening contributes to BP lability with load alteration in HFpEF (10,12,19). We observed that the pulsatile components of arterial afterload were greater in HFpEF as compared with HFrEF (Fig. 1), confirming and extending upon prior noninvasive studies (20). The drop in arterial pressure with Ea reduction was steeper in HFpEF compared with HFrEF (Fig. 3B), indicating a higher afterload dependency of BP in HFpEF. Enhanced pressure sensitivity with load alteration is known to be present in normal aging (19), and similar to epidemiologic studies (20), HFpEF patients were older than HFrEF patients in the current study. However, each of the observed differences in pressure and flow responses with nitroprusside persisted after adjusting for age, sex, and body size.

Diastolic responses to vasodilation in HF. Despite marked peripheral hemodynamic differences with nitroprusside, central cardiac pressures dropped to a similar extent on average in HFpEF and HFrEF, though HFpEF patients were more likely to experience a drop in SV. Afterload elevation prolongs diastolic relaxation (21), and it is thought that vasodilation may correspondingly enhance diastolic function (14,22). Somewhat surprisingly, there was no relationship between the change in BP or Ea and the extent of reduction in filling pressures, suggesting a less direct role for afterload-mediated effects on diastolic function in this study.

Nitroprusside is considered to be predominantly an arterial vasodilator (6), although venodilator effects play an important role in reducing LV filling pressures (7). In the current study, the drop in Ea was similar in both groups, but HFpEF patients were more likely to have a reduction in SV, and the enhancement in SV as a function of LV filling pressures was lower in HFpEF than HFrEF (Figs. 3A and 3C). Because LV end-systolic volume is unlikely to increase with afterload reduction, the drop in SV with nitroprusside by default was almost certainly due to a decrease in LV end-diastolic volume (preload). SV reduction with nitroprusside was observed in 35% of HFpEF patients compared with only 9% of HFrEF patients, despite the presence of elevated filling pressures in both groups. This finding suggests that HFpEF patients were more likely to be operating closer to the "shoulder" of their Starling curves, where further reduction in filling pressure limits SV and stroke work. That could make HFpEF patients more vulnerable to deleterious effects of vasodilation.

Reduction in LV filling pressure with nitrates are complex and may be due to improvement in afterload-dependent relaxation delay, decrease in chamber volume from venodilation, acute improvement in diastolic compliance, or relief of pericardial constraint (6,7,23–25). Absent volume data obtained at the time of catheterization, we cannot determine the relative roles these mechanisms played in the current study.

Right-sided circulation. Given the lower operating pressures in the pulmonary circulation, the right ventricle (RV) is poorly adapted to pressure overload, and similar to the LV in HFrEF, the RV is exquisitely sensitive to acute changes in afterload (26). Indeed, the presence of pulmonary hypertension is a potent predictor of mortality in HFrEF and HFpEF (27,28), and pulmonary vasodilators are being tested in both forms of HF. Chronic elevation in left-sided filling pressures raises pulmonary pressure and can lead to secondary pulmonary arterial hypertension and right-side heart failure (27), yet it is unknown whether this progression affects patients with HFrEF and HFpEF differently. In the current study, patients with HFrEF were more likely to display RV systolic dysfunction by echocardiography, despite similar mean pulmonary artery pressure and resistance. The drop in pulmonary artery systolic pressure with vasodilation was attenuated in HFrEF compared with HFpEF (Fig. 3D), suggesting that RV Ees is also greater in HFpEF compared with HFrEF on average, although the disparities in response to vasodilation were less dramatic than those observed in the systemic circulation.

Implications for treatment. Vasodilators targeting the renin-angiotensin system produce unequivocal benefit in HFrEF, related to both vasorelaxation properties and blockade of maladaptive neurohormonal signaling, yet several large clinical trials have failed to demonstrate similar benefit in HFpEF (3–5). The diverging hemodynamic responses noted in the current study may explain part of this disparity, while allowing clinicians to better anticipate effects of vasodilators in the individual HF patient. For example, excessive reduction in BP or SV with vasodilation in HFpEF could potentially offset any benefit from antagonism of pathologic neurohormonal activation, particularly among the elderly where orthostatic tolerance and vascular stiffening are more problematic (19). Despite the negative trials, vasodilators are sometimes prescribed for HFpEF in the absence of other compelling indications on the basis of their established efficacy for HFrEF. The current findings

raise questions with this practice, although clearly patients with HFpEF and uncontrolled hypertension may benefit from vasodilators.

Study limitations. This study is limited by its retrospective nature, cross-sectional design, and catheterization laboratory referral population. The sample is limited to patients who received nitroprusside, suggesting possible bias, although in our laboratory it is routine to administer nitroprusside to all patients in whom left heart filling pressures are elevated, regardless of EF. Echocardiography was performed before catheterization, and simultaneous volumetric data were not available, limiting direct measurements of pressure volume relationships. LV Ees was estimated using non-simultaneous echocardiographic volume data and assuming zero volume intercept in all patients, with no change in end-diastolic volume or parallel shift in Ees with nitroprusside (Fig. 4). On the basis of prior studies, it is likely that these assumptions were frequently violated (7,9,29). However, the goal of the study was simply to determine whether the central and peripheral hemodynamic responses categorically differ in HFpEF and HFrEF, and these exploratory analyses were conducted to examine the possible hemodynamic underpinnings for the observed differences. The HFpEF group studied was hypertensive (median systolic BP 166 mm Hg), and these results may not apply to patients with better BP control. Cardiac output was not assessed during nitroprusside in all cases, although pressure data were available for all, and characteristics of patients with and without output reassessment were similar.

Conclusions

Although HFpEF and HFrEF share many similarities in terms of clinical presentation and outcomes, important differences exist in pathophysiology and response to therapy. Whereas hemodynamic abnormalities at rest are similar in HFpEF and HFrEF, the 2 HF phenotypes display markedly different responses to vasodilation related to fundamental, disease-specific differences ventricular-arterial properties—with greater BP reduction in HFpEF and more SV enhancement in HFrEF. These data provide further evidence justifying the distinction of HFpEF and HFrEF as separate HF phenotypes, and they suggest that alternative treatment strategies targeted to ventricular-vascular stiffening rather than afterload reduction may have greater likelihood of benefit in HFpEF.

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Key Words: heart failure ■ treatment ■ vasodilation ■ ventricular function ■ ventricular-arterial interaction.

APPENDIX

For supplemental tables, please see the online version of this article.