Hemodynamic Responses to Rapid Saline Loading

The Impact of Age, Sex, and Heart Failure

Naoki Fujimoto, MD, PhD; Barry A. Borlaug, MD; Gregory D. Lewis, MD; Jeffrey L. Hastings, MD; Keri M. Shafer, MD; Paul S. Bhella, MD; Graeme Carrick-Ranson, PhD; Benjamin D. Levine, MD

Background**—**Hemodynamic assessment after volume challenge has been proposed as a way to identify heart failure with preserved ejection fraction. However, the normal hemodynamic response to a volume challenge and how age and sex affect this relationship remain unknown.

Methods and Results**—**Sixty healthy subjects underwent right heart catheterization to measure age- and sex-related normative responses of pulmonary capillary wedge pressure and mean pulmonary arterial pressure to volume loading with rapid saline infusion (100–200 mL/min). Hemodynamic responses to saline infusion in heart failure with preserved ejection fraction (n=11) were then compared with those of healthy young (<50 years of age) and older (≥50 years of age) subjects. In healthy subjects, pulmonary capillary wedge pressure increased from 10±2 to 16±3 mm Hg after ~1 L and to 20±3 mm Hg after ~2 L of saline infusion. Older women displayed a steeper increase in pulmonary capillary wedge pressure relative to volume infused (16±4 mm Hg·L^{-1}·m^2) than the other 3 groups (*P*≤0.019). Saline infusion resulted in a greater increase in mean pulmonary arterial pressure relative to cardiac output in women compared with men regardless of age. Subjects with heart failure with preserved ejection fraction exhibited a steeper increase in pulmonary capillary wedge pressure relative to infused volume (25±12 mm Hg·L^{-1}·m^2) than healthy young and older subjects (*P*≤0.005).

Conclusions**—**Filling pressures rise significantly with volume loading, even in healthy volunteers. Older women and patients with heart failure with preserved ejection fraction exhibit the largest increases in pulmonary capillary wedge pressure and mean pulmonary arterial pressure. **(*Circulation*. 2013;127:55-62.)**

Key Words: age and sex difference ■ filling pressure ■ heart failure ■ stroke volume ■ volume loading

Intravenous volume infusion increases left ventricular (LV) end-diastolic volume and filling pressures,[1] which may be used diagnostically in certain patient populations. Heart failure with preserved ejection fraction (HFpEF) is often observed in elderly women with increased LV stiffening and/or prolonged relaxation but may be challenging to diagnose, even with invasive hemodynamic data.[2] Diagnostic guidelines recommend rapid volume challenge or exercise testing to distinguish patients with pulmonary arterial hypertension, who may experience modest increases in pulmonary capillary wedge pressure (PCWP), from those with HFpEF.[3] However, there are limited data on what represents a normal versus pathological response of PCWP to volume infusion.[4] Similarly, normative data on how pulmonary arterial pressures respond to increased blood flow and increased left-side filling pressures with saline infusion are lacking.

Clinical Perspective on p 62

Healthy sedentary aging leads to cardiovascular stiffening, resulting in impairment of LV diastolic function (prolonged LV relaxation and decreased LV compliance) and vascular function.[5–8] In addition, there is sexual dimorphism in the LV geometric and functional changes with normal aging.[9] A greater decline in long-axis velocities, a prolonged time to peak apical rotation during diastole,[10] and increased LV stiffness through the use of invasive[11] and noninvasive techniques[12] have been reported in healthy older women compared with men, suggesting that women are more likely to experience a reduction in LV diastolic function with age. Therefore, we speculate that these age- and sex-related changes in LV diastolic function may contribute to a greater increase in LV filling pressure during rapid saline infusion in older subjects compared with younger subjects, especially in women.

Therefore, the purposes of this study were to characterize the normal hemodynamic response to rapid saline infusion in healthy subjects, to evaluate age- and sex-related differences in this response, and to compare the changes in LV filling and mean pulmonary arterial pressure (MPAP) during saline infusion in healthy subjects with those in HFpEF patients.

Received April 26, 2012; accepted November 7, 2012

From the University of Texas Southwestern Medical Center at Dallas (N.F., J.L.H., K.M.S., P.S.B., G.C.-R.; B.D.L.); Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital, Dallas (N.F., J.L.H., K.M.S., P.S.B., G.C.-R.; B.D.L.); Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic Rochester, MN (B.A.B.); and Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston (G.D.L.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.112.111302/-/DC1.

Correspondence to Benjamin D. Levine, MD, Institute for Exercise and Environmental Medicine, 7232 Greenville Ave, Ste 435, Dallas, TX 75231. E-mail BenjaminLevine@TexasHealth.org

Methods

Sixty healthy subjects (30 men, 30 women; age, 21–77 years) were prospectively enrolled from the Dallas Heart Study, a population-based probability sample of individuals in the Dallas community or a second random sample of employees of Texas Health Resources as previously reported.[5] Eleven HFpEF patients (≥65 years of age) were prospectively enrolled as previously reported.[13] This study consists of 2 experiments. Experiment 1 was performed to evaluate the effects of age and sex on hemodynamic changes after rapid saline infusion in healthy subjects; experiment 2 was performed to evaluate hemodynamic changes after rapid saline infusion in HFpEF patients.

Study Subjects

Sixty healthy sedentary subjects were stratified into 4 groups according to age and sex: young (<50 years of age) men (n=13), older (≥50 years of age) men (n=17), young women (n=13), and older women (n=17). Subjects were excluded if they were exercising for ≥30 minutes >2 times per week. All subjects were rigorously screened for comorbidities, including obesity, lung disease, hypertension, LV wall thickness ≥12 mm, coronary artery disease, or structural heart disease at baseline and by postexercise transthoracic echocardiograms. All subjects signed an informed consent form, which was approved by the institutional review boards of the University of Texas Southwestern Medical Center at Dallas and Texas Health Presbyterian Hospital Dallas.

Eleven rigorously screened HFpEF patients (4 men, 7 women) were enrolled as previously reported.[13] HFpEF patients were defined as having a clear history of HF by Framingham criteria plus confirmatory evidence of pulmonary congestion by chest radiography, biomarker elevation, or catheterization, plus an ejection fraction >50% at the time of their index hospitalization.[13] Hemodynamic responses to rapid saline infusion were evaluated in HFpEF patients and were compared with those in healthy young and older subjects in experiment 1. Because there were more women in the HFpEF group, healthy subjects were randomly selected to match this male/female ratio in experiment 2 and were stratified into 2 groups: young (<50 years of age; 7 men, 13 women) and older (≥50 years of age; 10 men, 17 women) subjects. Diuretics and β-blockers were withheld on the morning of the study in HFpEF patients and were continued as soon as the study was completed.

Experimental Protocol

Protocols for experiments 1 and 2 are shown in Figure 1. A 6F Swan-Ganz catheter was placed from an antecubital vein under fluoroscopic guidance to measure PCWP, MPAP, and right atrial pressure (RAP).[13] Correct position of the Swan-Ganz catheter was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms.[5,13] Baseline measurements of PCWP, MPAP, heart rate, and cardiac output were performed. Cardiac output was measured by a modification of the acetylene rebreathing method.[5,14] Stroke volume (SV) was determined by cardiac output divided by heart rate.

After baseline data were acquired, warm isotonic saline was infused through an 18-gauge intravenous cannula placed from the antecubital vein facilitated at a rate of ~200 mL/min by the use a pneumatic sleeve compressing the infusate. In some cases, a 20-gauge cannula from antecubital or peripheral vein was used when an 18-gauge cannula could not be placed, resulting in a slightly slower rate of infusion (100–150 mL/min). Heart rate, MPAP, and RAP were recorded continuously during saline infusion. Hemodynamic measurements were repeated after each of the 2 stages of rapid saline infusion as described below.

Saline Infusion Protocol

In experiment 1, 2 stages of rapid saline infusion were performed (Figure 1). Immediately after 10 to 15 mL/kg of warm isotonic saline (NS1) was infused, PCWP and MPAP were recorded, followed by measurements of cardiac output within 2 minutes. Saline infusion was continued at ~10 mL/min after the first rapid infusion period (NS1) to maintain cardiac filling pressures at steady levels during NS1 measurements. Then, a second dose of saline was infused at the same rate (NS2), followed by repeat hemodynamic measurements. For ease of data comparison, the volume of saline indexed to body mass during NS1 was matched in men and women (13.7±1.6 versus 13.6±1.5 mL/kg). The absolute volume of saline infused during NS1 was similar between young and older men (1.10±0.16 and 1.11±0.18 L) or between young and older women (0.87±0.12 and 0.87±0.14 L).

In experiment 2, 1 stage of saline infusion was performed at a similar rate, followed by hemodynamic measurements (Figure 1). In HFpEF patients, the volume of infused saline was 0.55±0.23 L (range, 0.30–1.0 L), which was smaller for safety reasons than those in young (0.95±0.17 L) and older (0.97±0.20 L) subjects. The volume of saline per body mass in HFpEF was 6.1±1.9 mL/kg, and in all subjects, the infusion was stopped if pulmonary arterial diastolic pressure reached ≥25 mm Hg.

Assessment of LV Morphology

Cardiac magnetic resonance images were obtained with a 1.5-T Philips NT scanner to evaluate LV mass, volume, and ratio of LV mass to volume within 1 week of the catheterization.[15] LV end-diastolic volume and mass were measured with a steady-state free precision imaging sequence as previous reported.[5,13] During cardiac catheterization, LV images were obtained by 2-dimensional echocardiography at all loading conditions and were analyzed by use of the modified Simpson method of disks.

Cardiac Catheterization Data

Because external constraints influence LV volumes and pressures,[16] LV end-diastolic transmural filling pressure (LVTMP) was calculated as PCWP minus RAP.[17,18] The PCWP and SV data were used to construct Starling (SV index/PCWP) curves. LV stroke work index was calculated as follows: (mean BP−PCWP)×SV index, where BP is blood pressure, by the acetylene rebreathing method.[19] LV preload/stroke work relationships were constructed, and the slopes of the LV preload/stroke work relationship were used to assess global LV systolic function. Total peripheral resistance index was calculated as follows: (brachial mean BP−RAP)×80/CI, where CI is cardiac index. Transpulmonary gradient was calculated as MPAP minus PCWP, and pulmonary vascular resistance index was determined as transpulmonary gradient times 80 divided by cardiac index.

Measurements of Blood Volume

Baseline red blood cell volume and total blood volume were measured by the carbon monoxide rebreathing method only in healthy subjects.[20–22] Briefly, at baseline, blood was drawn to assess hematocrit and venous carboxyhemoglobin levels. After administration of a priming dose of 99% carbon monoxide, a second dose of carbon monoxide was administered. Blood samples were collected 10 minutes after each administration of carbon monoxide, and percent venous carboxyhemoglobin was measured with a diode-array spectrophotometer. The typical error for blood volume by this method in our laboratory is <3%.[21]

Statistical Analysis

Statistical analyses were performed with commercially available software. Data are expressed as mean±SD in tables and as mean±SE in figures. Baseline hemodynamic and pressure data were analyzed by 1-way ANOVA or ANCOVA with post hoc analysis, and the Kruskal-Wallis test was used for nonnormally distributed data. For data obtained during saline infusion, 2-way repeated measures ANOVA with Tukey post hoc analysis was applied to determine the main effects for group, loading condition, and interaction and to evaluate the differences between groups. A linear regression analysis was used to evaluate the relations between age and hemodynamic variables.

Changes in PCWP, RAP, LVTMP, and MPAP relative to infused saline during NS1 were assessed by the slopes of PCWP/saline, RAP/saline, LVTMP/saline, and MPAP/saline relationships. The relationship between MPAP and cardiac index augmentation was used to evaluate MPAP response patterns to increased blood flow into the pulmonary vasculature during NS1.[23] A value of $P<0.05$ was considered significant.

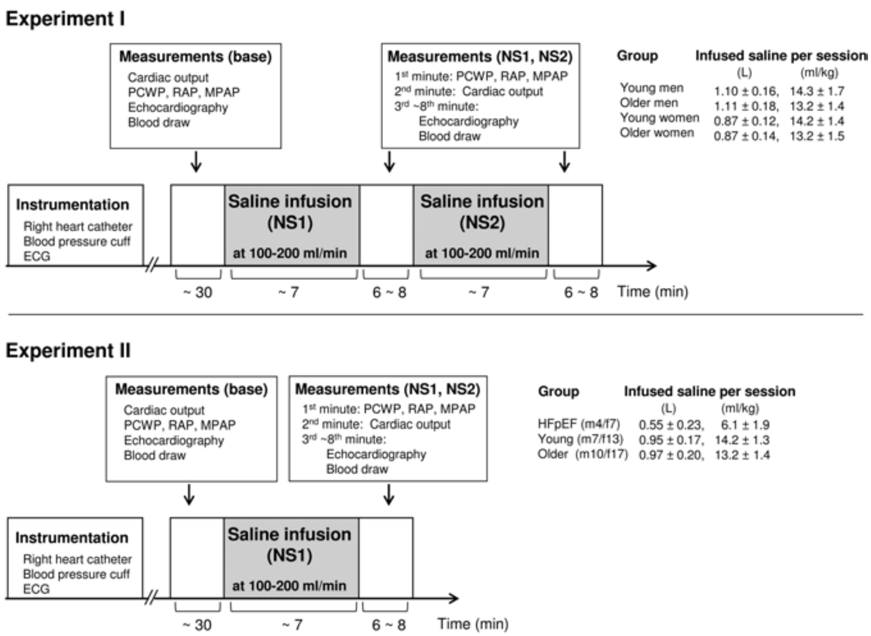


Figure 1. Protocols for experiments 1 and 2. HFpEF indicates heart failure with preserved ejection fraction; MPAP, mean pulmonary arterial pressure; NS1 and NS2, first and second sets of saline infusions; PCWP, pulmonary capillary wedge pressure; and RAP, right atrial pressure.

Results

Experiment 1

Ventricular Structure and Hemodynamics at Rest

LV end-diastolic volume and mass were lower in older women compared with young and older men (Table 1). A modest inverse correlation was observed between baseline PCWP and age in men but not in women (Figure I in the online-only Data Supplement).

Blood Volume Measurements

Red blood cell volume indexed to body mass was smaller in women than in men. There were no differences in red blood cell volume or total blood volume by age within the same sex (Figure II in the online-only Data Supplement). The amounts of saline infused during NS1 relative to the total blood volume in young men, older men, young women, and older women were 0.21±0.03, 0.20±0.03, 0.22±0.02, and 0.22±0.02, respectively (ANOVA P=0.090).

Hemodynamic Responses to Saline Infusion in Healthy Subjects

Heart rate and SV significantly increased after NS1 but not after NS2 in all 4 groups (Figure 2 and Table I in the online-only Data Supplement). Mean BP increased slightly after NS2 compared with baseline, resulting in decreases in total peripheral resistance index in all 4 groups with saline infusion.

Global LV systolic function assessed by the slope of preload/stroke work relations appeared to be similar between groups (Figure IIIA in the online-only Data Supplement). The Starling curves in young and older men showed a larger SV index at any given PCWP than those in young women during saline infusion (Figure IIIB in the online-only Data Supplement).

Rapid saline infusion significantly increased average PCWP in healthy subjects from 10±2 to 16±3 mm Hg (NS1) and 20±3 mm Hg (NS2; P<0.001; Figure 2). A slower rate of saline infusion (100–150 mL/min) in young women resulted in an increase in PCWP similar to that after saline infusion at a rate ≥150 mL/min (Table II in the online-only Data Supplement). A PCWP >15 mm Hg, which has previously been proposed as a partition value for defining elevated LV filling pressures,[3] was observed in 62% of the healthy subjects after NS1 and 93% of the subjects after NS2.

As shown in Figure 3, the increase in PCWP for any volume of saline infused was greater in older women compared with each of the other 3 groups by both absolute infused volume and volume indexed to body surface area, suggesting a lower diastolic reserve during rapid volume expansion in older women (Figure 3C and 3D). When the baseline PCWP and the amount of saline relative to the absolute total blood volume were used as covariates, 1-way ANCOVA still showed a steeper PCWP/saline slope in older women than the other 3 groups (P≤0.01). A greater increase in RAP relative to saline was also observed in older women compared with older men (10±2 versus 7±1 mm Hg·L^{-1}·m^{2}; P<0.001). The increase in LVTMP in older women was not statistically different from those in the other 3 groups (ANOVA P=0.157). As shown in Figure 3C and 3D, the slope describing the increase in PCWP relative to saline infused increased markedly with age in women but not men (age-by-sex interaction effect, P=0.01 in Figure 3C and 3D).

In contrast to the modest increase in systemic arterial BP, there were significant increases in MPAP (~80%) and transpulmonary gradient (~50%) in all 4 groups (Figure 2 and Table I in the online-only Data Supplement). Although overall changes in pulmonary vascular resistance index were similar among the 4 groups, pulmonary vascular resistance index appeared to increase slightly in only young and older women (Table I in the online-only Data Supplement).

The MPAP/saline relation in older women was significantly steeper than slopes observed in young and older men (Figure 4A). Young women also had a tendency toward a steeper slope of the MPAP/saline relation compared with men. There were significant sex disparities in the increase in MPAP relative to cardiac index (ANOVA P≤0.018; Figure 4B). Women had greater MPAP/cardiac index slopes

Table 1. Subjects' Characteristics: Experiment 1

	Young Men (n=13)	Older Men (n=17)	Young Women (n=13)	Older Women (n=17)	P, ANOVA
Age, y	33±7	62±8*	37±9†	64±5*‡	<0.001
Body weight, kg	78±11	83±8	62±7*†	66±9*†	<0.001
Body surface area, m^2	1.94±0.19	2.03±0.11	1.68±0.12*†	1.74±0.13*†	<0.001
Hemodynamics (supine rest)					
Heart rate, bpm	75±8	66±7*	83±10*†	72±7‡	<0.001
Mean BP, mm Hg	81±4	82±8	80±13	79±9	0.723
Cardiac index (reb), L·min^{-1}·m^{-2}	3.34±0.45	2.97±0.40	3.14±0.68	2.89±0.38	0.082
SV index (reb), mL/m^2	45.2±7.4	45.5±8.5	37.9±6.5*†	40.4±4.0†	0.010
MPAP, mm Hg	16±2	15±4	16±3	15±2	0.968
Mean PCWP, mm Hg	11±2	9±2	10±2	10±2	0.119
RAP, mm Hg	7±2	6±2	6±1	7±1	0.448
LVTMP, mm Hg	4±1	3±1*†	4±1	3±1*†	0.002
Transpulmonary gradient, mm Hg	5±1	6±2	6±3	6±2	0.368
Ventricular structure (MRI)					
LVEDV index, mL/m^2	65.6±6.8	63.3±10.5	58.1±7.1	52.0±8.5*†	<0.001
LVESV index, mL/m^2	22.5±5.0	19.3±5.8	19.4±4.7	14.8±4.4*	0.001
LV mass index, g/m^2	60.1±7.3	56.1±6.6	51.9±11.6*	43.7±6.0*†	<0.001

BP indicates blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular; MPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; reb, by acethylene rebreathing method; SV, stroke volume; and TMP, transmural pressure. Values are mean±SD.

*P<0.05 versus young men.

†P<0.05 versus older men.

‡P<0.05 versus young women.

than men (P≤0.065), but within the sexes, there was no age-related differences in MAP/cardiac index slopes (P>0.50 for men and women).

Experiment 2

HFpEF patients were heavier and had higher BP. LV mass index and the ratio of LV mass to end-diastolic volume were significantly greater in HFpEF patients compared with healthy control subjects, suggesting concentric remodeling in HFpEF. In these stable outpatients with HFpEF, mean PCWP at supine rest was relatively controlled; nevertheless, mean PCWP, RAP, and LVTMP were all significantly higher in HFpEF patients than in young and older subjects (Table 2). Because of the risk of precipitating heart failure decompensation, the total and body size–normalized volume of saline administered was lower in HFpEF than in control subjects (Figure 1 and Table 3). Similar to healthy subjects, saline infusion increased SV index, MPAP, PCWP, and RAP in HFpEF patients. After NS1, a slight increase or no change in RAP with inspiration (Kussmaul sign) was observed in >60% of the HFpEF patients and healthy control subjects, suggesting increased pericardial constraint. No HFpEF patients developed overt symptoms of heart failure during or after saline infusion.

As shown in Figure 5, the slope of the PCWP/saline relation was steeper in HFpEF than in healthy young and older subjects. When analyzed individually, HFpEF patients exhibited a steeper PCWP/saline slope (25±12 mm Hg·L^{-1}·m^2) than young and older subjects (12±3 and 14±5 mm Hg·L^{-1}·m^2; P≤0.005). When the baseline PCWP was used as a covariate, 1-way ANCOVA still exhibited a steeper PCWP/saline slope in HFpEF than young and older subjects (P<0.001).

Compared with healthy young and older subjects, HFpEF patients also had steeper RAP/saline slope (13±3 versus 8±2 and 9±2 mm Hg·L^{-1}·m^2; P<0.001) and LVTMP/saline slope (12±10 versus 4±3 and 5±4 mm Hg·L^{-1}·m^2; P≤0.085). The RAP/saline slopes were significantly correlated to the PCWP/saline slopes in HFpEF patients, healthy young subjects, and older subjects (R^2=0.466, 0.211, and 0.379; P≤0.041). No difference was observed in PAP/saline slope among the 3 groups (ANOVA P=0.137).

Discussion

We demonstrate for the first time in healthy humans that rapid saline infusion increases filling pressures more in older women compared with men and younger women. More than 90% of normal volunteers were found to display increases in PCWP to values previously considered to define HFpEF (>15 mm Hg) with ~2 L saline.[3,24] In addition, the greatest increase in PCWP with saline infusion was noted in HFpEF, consistent with impaired diastolic reserve. Finally, the lower diastolic volume loading reserve observed in older women offers novel insight into the greater predilection for older-aged women to develop HFpEF.

PCWP Responses to Rapid Saline Infusion in Healthy Subjects

In animals, increases in LV end-diastolic pressure and volume after rapid volume challenge have been reported.[1,25] To the best of our knowledge, 1 study has evaluated PCWP changes during saline infusion in healthy humans.[4] Contrary to our results, Kumar et al[4] observed only a modest increase in PCWP after infusion at a rate of 1 L/h. With such a slow

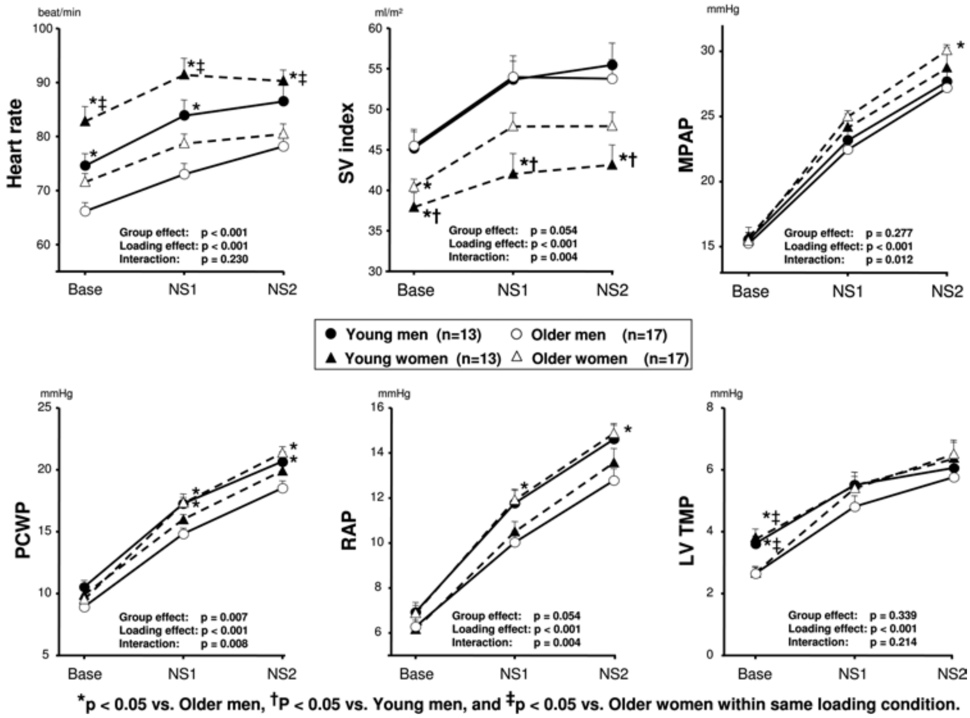


Figure 2. Changes in heart rate, stroke volume (SV) index, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), and left ventricular end-diastolic transmural filling pressure (LVTMP) during rapid saline infusion. Two-way repeated measures ANOVA with post hoc analysis was used. NS1 and NS2 indicate first and second sets of saline infusions. ● Indicates young men; ○, older men; ▲, young women; and Δ, older women. *$P<0.05$ vs older men, †$P<0.05$ vs young men, and ‡$P<0.05$ vs older women within the same loading condition.

rate, fluid is more likely to move from the central circulation to interstitial spaces[26] or to be redistributed into the venous capacitance vessels,[27] resulting in a blunted PCWP increase.

Effects of Age and Sex on PCWP During Rapid Saline Infusion

Age increased the gain in filling pressures with saline infusion in older women. Volume loading shifts the operating point on the curvilinear LV end-diastolic pressure-volume relation to a steeper position[28]; thus, the absolute increase in PCWP relative to saline infusion could be accentuated in subjects with steep end-diastolic pressure-volume relations. Pericardial constraint significantly elevates LV filling pressure and influences LV chamber compliance.[16,29] In this study, the Kussmaul sign was observed in >60% of the control subjects and HFpEF patients. In most cases, the PCWP demonstrated greater A and V waves with no prominent y descent, consistent with coupled pericardial constraint.[30] In older women, a greater increase in RAP was observed during infusion, whereas the increase in LVTMP was not different from those in other groups. These findings may suggest that LV hemodynamics in older women are more affected by

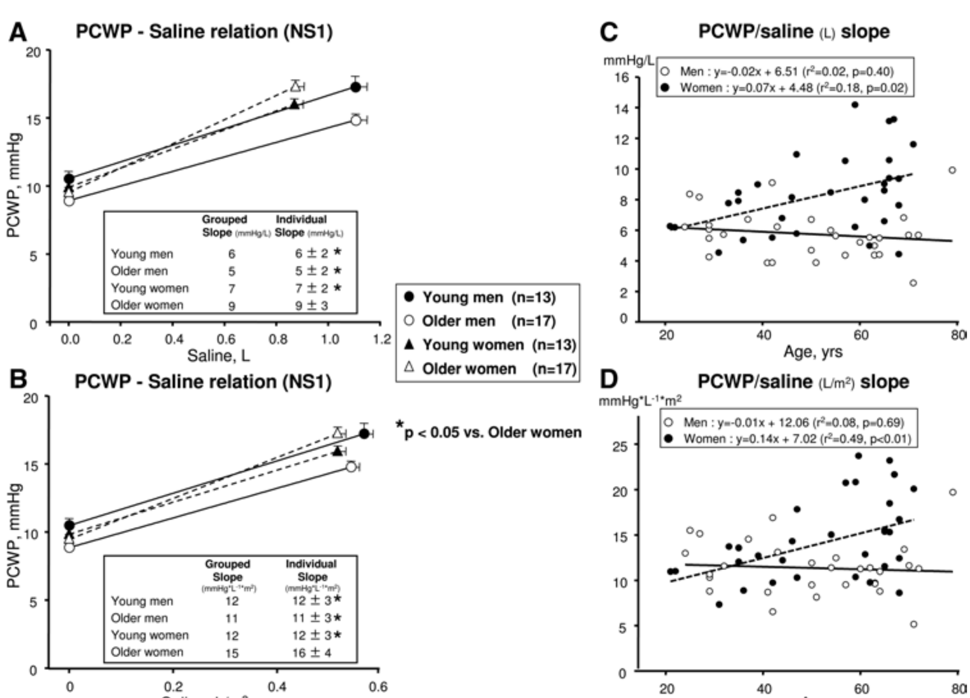


Figure 3. **A** and **B**, Pulmonary capillary wedge pressure (PCWP) relative to saline after the first set of saline infusions (NS1; top left) and the relationship between PCWP/saline slope and age (top right). **C** and **D**, PCWP relative to saline after NS1 (bottom left) and the relationship between PCWP/saline slope and age in healthy subjects (bottom right). The graphs on the bottom display indexed values. ● Indicates young men; ○, older men; ▲, young women; and Δ, older women. *$P<0.05$ vs older women.

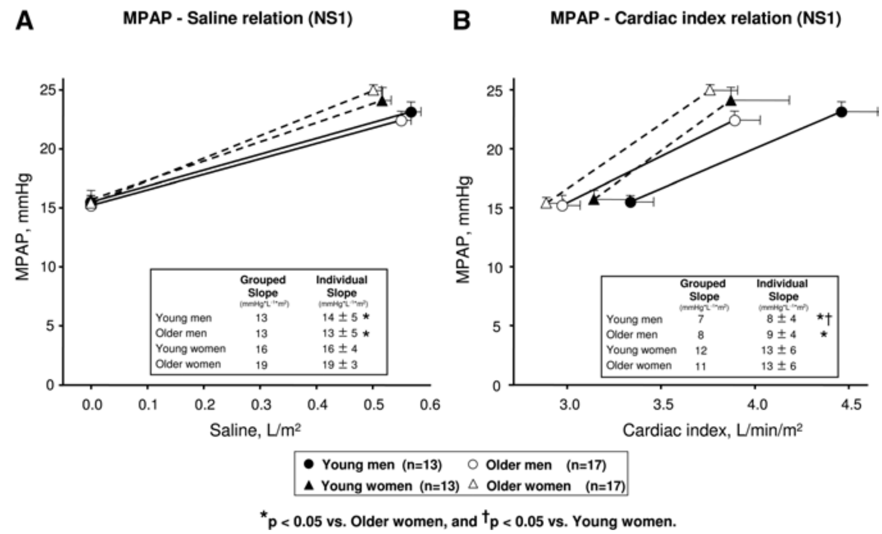


Figure 4. **A**, Mean pulmonary arterial pressure (MPAP) relative to saline after the first set of saline infusions (NS1) in healthy subjects (left). ●Indicates young men; ○, older men; ▲, young women; and Δ, older women. **P*<0.05 vs older women. **B**, MPAP relative to cardiac index after NS1. **P*<0.05 vs older women; †*P*<0.05 vs young women.

pericardial constraint. HFpEF patients are more likely to be older women with hypertension and diabetes mellitus.[31] Therefore, our findings may partly explain this age and sex predilection in the HFpEF population.

Table 2. Subjects' Characteristics: Experiment 2

	Young (n=20)	Older (n=27)	HFpEF (n=11)	P, ANOVA
Female, n (%)	13 (65)	17 (63)	7 (64)	0.990
Age, y	36±8	64±6*	73±7*†	<0.001
Body weight, kg	68±12	73±12	89±21*†	0.001
Body surface area, m²	1.78±0.19	1.86±0.20	1.99±0.27*	0.032
Hemodynamics (supine rest)				
Heart rate, bpm	80±10	70±7*	76±21	0.002
Systolic BP, mm Hg	114±14	113±13	141±20*†	<0.001
Mean BP, mm Hg	81±10	81±9	92±9*†	0.001
Cardiac index (reb), L·min⁻¹·m⁻²	3.24±0.59	2.97±0.35	3.27±1.19	0.285
SV index (reb), mL/m²	40.4±6.8	42.7±5.3	42.7±8.3	0.454
MPAP, mm Hg	15±3	15±2	24±4*†	<0.001
Mean PCWP, mm Hg	10±2	9±2	14±4*†	0.002
RAP, mm Hg	6±2	7±2	9±3*	0.036
LVTMP, mm Hg	4±1	3±1*	5±3†	<0.001
Transpulmonary gradient, mm Hg	6±2	6±2	10±3*†	<0.001
Ventricular structure (MRI)				
LVEDV index, mL/m²	60.8±7.5	56.0±10.8	56.3±12.1	0.236
LVESV index, mL/m²	21.1±5.3	16.3±4.8*	14.3±5.5*	0.002
LV mass index, g/m²	54.7±11.0	47.1±7.4	69.3±21.8*†	<0.001
LV mass/EDV, g/mL	0.89±0.20	0.86±0.13	1.23±0.32*†	<0.001

BP indicates blood pressure; EDV, end-diastolic volume; ESV, end-systolic volume; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; MPAP, mean pulmonary arterial pressure; MRI, magnetic resonance imaging; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; reb, by acethylene rebreathing method; SV, stroke volume; and TMP, transmural pressure. Values are mean±SD.

**P*<0.05 versus young.

†*P*<0.05 versus older.

Saline Loading Responses in HFpEF

Greater PCWP/saline slopes were observed in HFpEF patients compared with healthy subjects. These findings indicate that HFpEF patients had increased LV stiffening and/or that the

Table 3. Hemodynamic Responses to Saline Infusion: Experiment 2

	Young (n=20)	Older (n=27)	HFpEF (n=11)
Saline infused during NS1, L	0.95±0.17	0.97±0.20	0.55±0.23*†
Saline infused during NS1, mL/kg	14.2±1.3	13.2±1.4	6.1±1.9*†
Heart rate, bpm			
Baseline	80±10	70±7*	76±21
NS1	89±11‡	77±7‡	78±17
Systolic BP, mm Hg			
Baseline	114±14	113±13	141±20*†
NS1	116±15	117±13‡	140±21
Cardiac index (reb), L/m²			
Baseline	3.23±0.59	2.97±0.40	3.14±0.68
NS1	4.03±0.99‡	3.87±0.54‡	3.87±1.22‡
SV index (reb), mL/m²			
Baseline	40.4±6.8	42.7±5.3	42.7±8.3
NS1	45.6±10.1‡	50.4±7.6‡	48.9±6.7‡
MPAP, mm Hg			
Baseline	15±3	15±2	24±4*†
NS1	23±4‡	24±2‡	30±3‡
Mean PCWP, mm Hg			
Baseline	10±2	9±2	14±4*†
NS1	16±2‡	17±2‡	20±4‡
RAP, mm Hg			
Baseline	6±2	7±2	9±3*
NS1	11±2‡	11±2‡	12±3‡

BP indicates blood pressure; MPAP, mean pulmonary arterial pressure; NS1, first session of saline infusion; NS2, second session of saline infusion; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; reb, by acetylene rebreathing technique; SV, stroke volume. Values are mean±SD.

**P*<0.05 versus young at baseline.

†*P*<0.05 versus older at baseline.

‡*P*<0.05 versus baseline for comparison of the effects of saline loading.

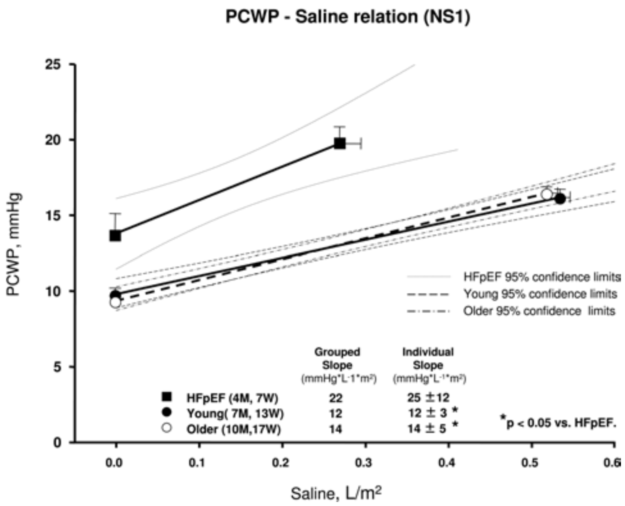


Figure 5. Pulmonary capillary wedge pressure (PCWP) relative to saline in patients with heart failure with preserved ejection fraction (HFpEF), young subjects, and older subjects after the first set of saline infusions (NS1). Dashed line indicates 95% confidence limits; ●, young subjects; ○, older subjects; and ■, HFpEF patients. *P<0.05 vs HFpEF patients.

ventricles were operating on the steeper portion of their pressure-volume relations during saline infusion. RAP is regulated mainly by pericardial constraint.[17] Thus, a greater RAP/saline slope in HFpEF may indicate that HFpEF patients are more affected by pericardial constraint than healthy older subjects. We also point out that LVTMP/saline slopes appeared to be greater in HFpEF patients than healthy control subjects (P≤0.085). These findings suggest that it is not exclusively the pericardium that causes the rise in filling pressures during saline infusion. Venodilation with nitroglycerin reduces pericardial constraint and lowers cardiac filling pressure.[29] Thus, nitroglycerin might be a reasonable therapeutic option in HFpEF patients with high levels of pericardial constraint.

Blood Volume/Plasma Volume Data

Total body blood volume can be stratified into the unstressed and stressed volumes in the arterial and nonsplanchnic systemic venous beds.[32] The largest absolute plasma and total blood volumes were observed in older men, whereas older men tended to have lower cardiac filling pressures compared with young men. We speculate that older men may have possessed a larger venous reservoir and/or smaller effective circulatory volume than other groups.

Invasive Hemodynamic Stress Testing

Volume challenge and exercise testing with right heart catheterization have been used to unmask diastolic dysfunction and to diagnose HFpEF.[3,24,33] In contrast to exercise testing, saline loading has minor effects on BP and HR and predominantly tests operant diastolic ventricular compliance. Saline infusion is more widely available than invasive exercise testing, and the present data may expand the capability to perform provocative invasive assessment to more laboratories. Intriguingly, we observed that rapid saline infusion had greater effects on the pulmonary circulation than previously reported during exercise.[23,34] We also observed that healthy women have a smaller reserve for flow-mediated pulmonary artery dilatation compared with men, which may predispose them to greater risk for pulmonary vascular disease with chronic left heart disease.[35,36]

Study Limitations

First, the number of our HFpEF patients was small, and the control group was free of any cardiovascular diseases. The power of the PCWP/saline slope analysis was 0.84 in experiment 1 and 0.70 in experiment 2. Future studies are required to assess how effectively saline loading differentiates patients with HFpEF from patients with other cardiovascular diseases such as systemic and pulmonary arterial hypertension. Second, saline was not infused at precisely the same rate in all subjects because of the inability to obtain large-bore cannulas. However, most catheterization laboratories do not have the capability to precisely regulate infusion rates. Moreover, the changes in hemodynamics, including PCWP, during saline infusion at a rate <150 mL/min were quite similar to those at a rate ≥150 mL/min in young women (Table II in the online-only Data Supplement). We believe that this range is relevant to clinical practice. Third, the total but not scaled volume of infused saline was lower in women than men and in HFpEF patients than control subjects. It is possible but unlikely that the initial increment in filling pressures was greater than increments with more volume because responses of filling pressures to rapid infusion were approximately linear (Figure 2). Fourth, blood volume was not measured in HFpEF patients. Differences in the preinfusion distribution of blood volume or the distribution of the infused saline within the systemic veins and regional venous capacitance vessels might have contributed to the observed differences within control subjects and between control subjects and HFpEF patients. Finally, there were differences in age between HFpEF and healthy older subjects and in body size among groups, which might have affected our results.

Conclusions

In healthy humans rigorously screened for cardiovascular disease, there are significant elevations in left and right heart filling pressures during rapid saline infusion, suggesting that currently proposed partition values of PCWP used to define "heart failure" from saline loading need to be revisited. The increase in PCWP during saline infusion was greatest in older women, suggesting more loss of diastolic and pericardial compliance reserve in the aged female heart compared with men and to younger control subjects.

Source of Funding

This study was supported by National Institutes of Health grant AG17479.

Disclosures

None.

References

1. Courtois M, Mechem CJ, Barzilai B, Gutierrez F, Ludbrook PA. Delineation of determinants of left ventricular early filling: saline versus blood infusion. *Circulation*. 1994;90:2041–2050.
2. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32:670–679.
3. Hoeper M, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM,

Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol*. 2009;54:S85–S96.
4. Kumar A, Anel R, Bunnell E, Habet K, Zanotti S, Marshall S. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med*. 2004;32:691–699.
5. Fujimoto N, Hastings JL, Bhella PS, Shibata S, Gandhi NK, Carrick-Ranson G, Palmer D, Levine BD. Effect of aging on left ventricular compliance and distensibility in healthy sedentary humans. *J Physiol*. 2012;590:1871–1880.
6. Hirota Y. A clinical study of left ventricular relaxation. *Circulation*. 1980;62:756–763.
7. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises, part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107:139–146.
8. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*. 2009;119:2663–2670.
9. Scantlebury DC, Borlaug BA. Why are women more likely than men to develop heart failure with preserved ejection fraction? *Curr Opin Cardiol*. 2011;26:562–568.
10. Föll D, Jung B, Schilli E, Staehle F, Geibel A, Hennig J, Bode C, Markl M. Magnetic resonance tissue phase mapping of myocardial motion: new insight in age and gender. *Circ Cardiovasc Imaging*. 2010;3:54–64.
11. Hayward CS, Kalnins WV, Kelly RP. Gender-related differences in left ventricular chamber function. *Cardiovasc Res*. 2001;49:340–350.
12. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation*. 2005;112:2254–2262.
13. Prasad A, Hastings JL, Shibata S, Popovic ZB, Arbab-Zadeh A, Bhella PS, Okazaki K, Fu Q, Berk M, Palmer D, Greenberg NL, Garcia MJ, Thomas JD, Levine BD. Characterization of static and dynamic left ventricular diastolic function in patients with heart failure and a preserved ejection fraction. *Circ Heart Fail*. 2010;3:617–626.
14. Laszlo G. Respiratory measurements of cardiac output: from elegant idea to useful test. *J Appl Physiol*. 2004;96:428–437.
15. Hundley WG, Li HF, Willard JE, Landau C, Lange RA, Meshack BM, Hillis LD, Peshock RM. Magnetic resonance imaging assessment of the severity of mitral regurgitation: comparison with invasive techniques. *Circulation*. 1995;92:1151–1158.
16. Dauterman K, Pak PH, Maughan WL, Nussbacher A, Ariê S, Liu CP, Kass DA. Contribution of external forces to left ventricular diastolic pressure: implications for the clinical use of the Starling law. *Ann Intern Med*. 1995;122:737–742.
17. Belenkie I, Kieser TM, Sas R, Smith ER, Tyberg JV. Evidence for left ventricular constraint during open heart surgery. *Can J Cardiol*. 2002;18:951–959.
18. Arbab-Zadeh A, Dijk E, Prasad A, Fu Q, Torres P, Zhang R, Thomas JD, Palmer D, Levine BD. Effect of aging and physical activity on left ventricular compliance. *Circulation*. 2004;110:1799–1805.
19. Glower DD, Spratt JA, Snow ND, Kabas JS, Davis JW, Olsen CO, Tyson GS, Sabiston DC Jr, Rankin JS. Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work. *Circulation*. 1985;71:994–1009.
20. Burge CM, Skinner SL. Determination of hemoglobin mass and blood volume with CO: evaluation and application of a method. *J Appl Physiol*. 1995;79:623–631.
21. Gore CJ, Hopkins WG, Burge CM. Errors of measurement for blood volume parameters: a meta-analysis. *J Appl Physiol*. 2005;99:1745–1758.
22. Gore CJ, Rodríguez FA, Truijens MJ, Townsend NE, Stray-Gundersen J, Levine BD. Increased serum erythropoietin but not red cell production after 4 wk of intermittent hypobaric hypoxia (4,000–5,500 m). *J Appl Physiol*. 2006;101:1386–1393.
23. Lewis GD, Murphy RM, Shah RV, Pappagianopoulos PP, Malhotra R, Bloch KD, Systrom DM, Semigran MJ. Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. *Circ Heart Fail*. 2011;4:276–285.
24. Champion HC. Getting more from right heart catheterization: a focus on the right ventricle. *Adv Pulm Hypertens*. 2008;7:343–345.
25. Fragata J, Areias JC. Effects of gradual volume loading on left ventricular diastolic function in dogs: implications for the optimisation of cardiac output. *Heart*. 1996;75:352–357.
26. Cecconi M, Parsons A, Rhodes A. What is a fluid challenge? *Curr Opin Crit Care*. 2011;17:290–295.
27. Tyberg JV, Hamilton DR. Orthostatic hypotension and the role of changes in venous capacitance. *Med Sci Sports Exerc*. 1996;28:S29–S31.
28. Burkhoff D, Mirsky I, Suga H. Assessment of systolic and diastolic ventricular properties via pressure-volume analysis: a guide for clinical, translational, and basic researchers. *Am J Physiol Heart Circ Physiol*. 2005;289:H501–H512.
29. Kingma I, Smiseth OA, Belenkie I, Knudtson ML, MacDonald RP, Tyberg JV, Smith ER. A mechanism for the nitroglycerin-induced downward shift of the left ventricular diastolic pressure-diameter relation. *Am J Cardiol*. 1986;57:673–677.
30. Tyberg JV. Invited editorial on "Coupled vs. uncoupled pericardial constraint: effects on cardiac chamber interactions." *J Appl Physiol*. 1997;83:1797–1798.
31. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259.
32. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance: redistribution of the venous reservoir as a cause of decompensation. *Circ Heart Fail*. 2011;4:669–675.
33. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3:588–595.
34. Lewis GD. Pulmonary vascular response patterns to exercise: is there a role for pulmonary arterial pressure assessment during exercise in the post-Dana Point era? *Adv Pulm Hypertens*. 2010;9:92–100.
35. Thenappan T, Shah SJ, Gomberg-Maitland M, Collander B, Vallakati A, Shroff P, Rich S. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2011;4:257–268.
36. Borlaug BA. Discerning pulmonary venous from pulmonary arterial hypertension without the help of a catheter. *Circ Heart Fail*. 2011;4:235–237.

CLINICAL PERSPECTIVE

A volume challenge unmasks left ventricular diastolic dysfunction and therefore has been proposed as a way to identify heart failure with preserved ejection fraction. However, the normal hemodynamic response to a volume challenge and how age and sex affect this relationship remain unknown. In the present study, we assessed age- and sex-related normative responses of pulmonary capillary wedge pressure to rapid saline infusion (100–200 mL/min) in 60 healthy subjects. Hemodynamic responses to saline infusion in 11 patients with heart failure with preserved ejection fraction were then compared with those in healthy young and older subjects. Rapid saline infusion significantly increased pulmonary capillary wedge pressure from 10±2 to 16±3 mm Hg with ~1 L saline and to 20±3 mm Hg with ~2 L saline in healthy subjects. More than 90% of the healthy subjects exhibited pulmonary capillary wedge pressure values previously considered to define heart failure with preserved ejection fraction (>15 mm Hg) with ~2 L saline. In older women, a greater increase in pulmonary capillary wedge pressure relative to volume infused was observed compared with men and younger women, suggesting more dramatic loss of diastolic reserve in older women. The greatest increase in pulmonary capillary wedge pressure relative to volume infused was noted in patients with heart failure with preserved ejection fraction, consistent with the most severely impaired diastolic reserve. These data could constitute an important step for the development of diagnostic protocols for the invasive evaluation of patients with dyspnea. Future studies will assess how effectively saline loading differentiates patients with heart failure with preserved ejection fraction from patients with other cardiovascular diseases such as systemic and pulmonary arterial hypertension.

Circulation

American Heart Association®

Hemodynamic Responses to Rapid Saline Loading: The Impact of Age, Sex, and Heart Failure

Naoki Fujimoto, Barry A. Borlaug, Gregory D. Lewis, Jeffrey L. Hastings, Keri M. Shafer, Paul S. Bhella, Graeme Carrick-Ranson and Benjamin D. Levine

Circulation. 2013;127:55-62; originally published online November 21, 2012;
doi: 10.1161/CIRCULATIONAHA.112.111302
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Supplemental Table 1.

Hemodynamic responses to saline infusion (*Experiment I*)

	Young men (n=13)	**Older men** (n=17)	**Young women** (n=13)	**Older women** (n=17)
Saline infused during NS1, ml/kg	14.3 ± 1.7	13.2 ± 1.4	14.2 ± 1.4	13.2 ± 1.5
Saline infused during NS1, L	1.10 ± 0.16	1.11 ± 0.18	0.87 ± 0.12	0.87 ± 0.14
Saline infused during NS1+NS2, ml/kg	28.5 ± 3.2	26.5 ± 2.3	28.4 ± 3.2	26.4 ± 3.0
Saline infused during NS1+NS2, L	2.21 ± 0.33	2.21 ± 0.31	1.75 ± 0.23	1.75 ± 0.28
Heart rate, beats/min				
Baseline	75 ± 8	66 ± 7	83 ± 10	72 ± 7
NS1	84 ± 11*	73 ± 8*	91 ± 11*	79 ± 7*
NS2	86 ± 11*	78 ± 9*†	90 ± 7*	80 ± 8*
Mean BP, mmHg				
Baseline	81 ± 4	82 ± 8	80 ± 13	79 ± 9
NS1	84 ± 7	85 ± 6*	82 ± 13	81 ± 9
NS2	87 ± 8*	88 ± 9*	87 ± 14*†	86 ± 9*†
Stroke volume index (reb), ml/m^2				
Baseline	45.2 ± 7.4	45.5 ± 8.5	37.9 ± 6.5	40.4 ± 4.0
NS1	53.7 ± 8.2*	54.0 ± 10.8*	42.0 ± 9.1*	47.9 ± 6.9*
NS2	55.5 ± 9.8*	53.8 ± 9.7*	43.1 ± 8.9*	47.0 ± 6.1*
TPR index, dyne*s*cm^{-5}*m^2				
Baseline	1791 ± 243	2078 ± 449	1811 ± 482	1990 ± 350
NS1	1322 ± 139*	1574 ± 264*	1300 ± 372*	1486 ± 314*
NS2	1245 ± 231*	1477 ± 300*	1281 ± 456*	1433 ± 306*
MPAP pressure, mmHg				
Baseline	16 ± 2	15 ± 4	16 ± 3	15 ± 2
NS1	23 ± 3*	22 ± 3*	24 ± 4*	25 ± 2*
NS2	28 ± 3*†	27 ± 4*†	29 ± 6*†	30 ± 2*†
Mean PCWP, mmHg				
Baseline	11 ± 2	9 ± 2	10 ± 2	10 ± 2
NS1	17 ± 3*	15 ± 2*	16 ± 1*	17 ± 2*

NS2	21 ± 3*†	19 ± 2*†	20 ± 2*†	21 ± 2*†
Right atrial pressure, mmHg				
Baseline	7 ± 2	6 ± 2	6 ± 1	7 ± 1
NS1	12 ± 2*	10 ± 2*	11 ± 2*	12 ± 2*
NS2	15 ± 2*†	13 ± 2*†	14 ± 2*†	15 ± 2*†
LVTMP, mmHg				
Baseline	4 ± 1	3 ± 1	4 ± 1	3 ± 1
NS1	6 ± 2*	5 ± 1*	5 ± 2*	5 ± 2*
NS2	6 ± 2*	6 ± 2*†	6 ± 2*	7 ± 2*†
Transpulmonary gradient, mmHg				
Baseline	5 ± 1	6 ± 2	6 ± 3	6 ± 2
NS1	6 ± 2	8 ± 2*	8± 4*	8 ± 2*
NS2	7 ± 2*	9 ± 2*	9 ± 6*	9 ± 2*
PVR index, dyne*s*cm^{-5}*m^{2}				
Baseline	121 ± 35	170 ± 56	150 ± 62	161 ± 38
NS1	109 ± 47	157 ± 33	173 ± 68	165 ± 39
NS2	122 ± 45	169 ± 47	173 ± 93	183 ± 43

Values are mean ± SD. NS1 indicates first session of saline infusion; NS2, second session of saline infusion; BP, blood pressure; (reb), by acetylene rebreathing technique; PCWP, pulmonary capillary wedge pressure; MPAP, mean pulmonary arterial pressure; LVTMP, left ventricular transmural pressure; PVR, pulmonary vascular resistance. *P < 0.05 vs. baseline and †P < 0.05 vs. NS1 for comparison of the effects of saline loading in healthy subjects.

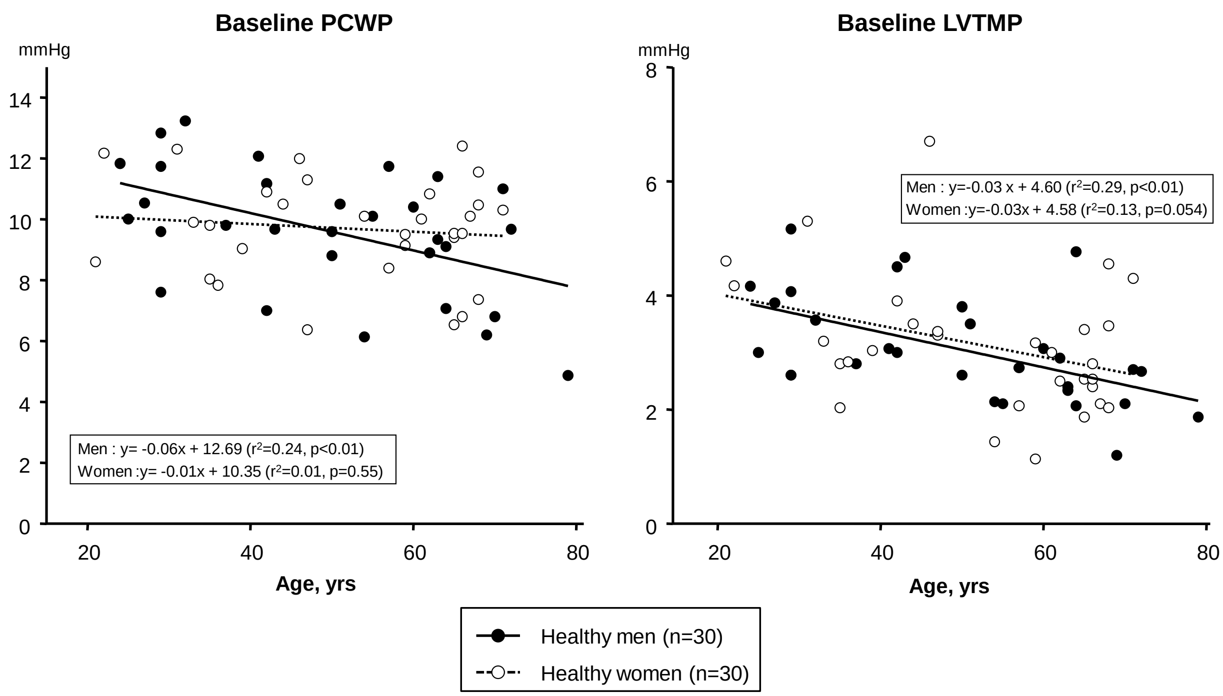
Supplemental Table 2.

Hemodynamics in young women with different rate of infusion (*Experiment I*)

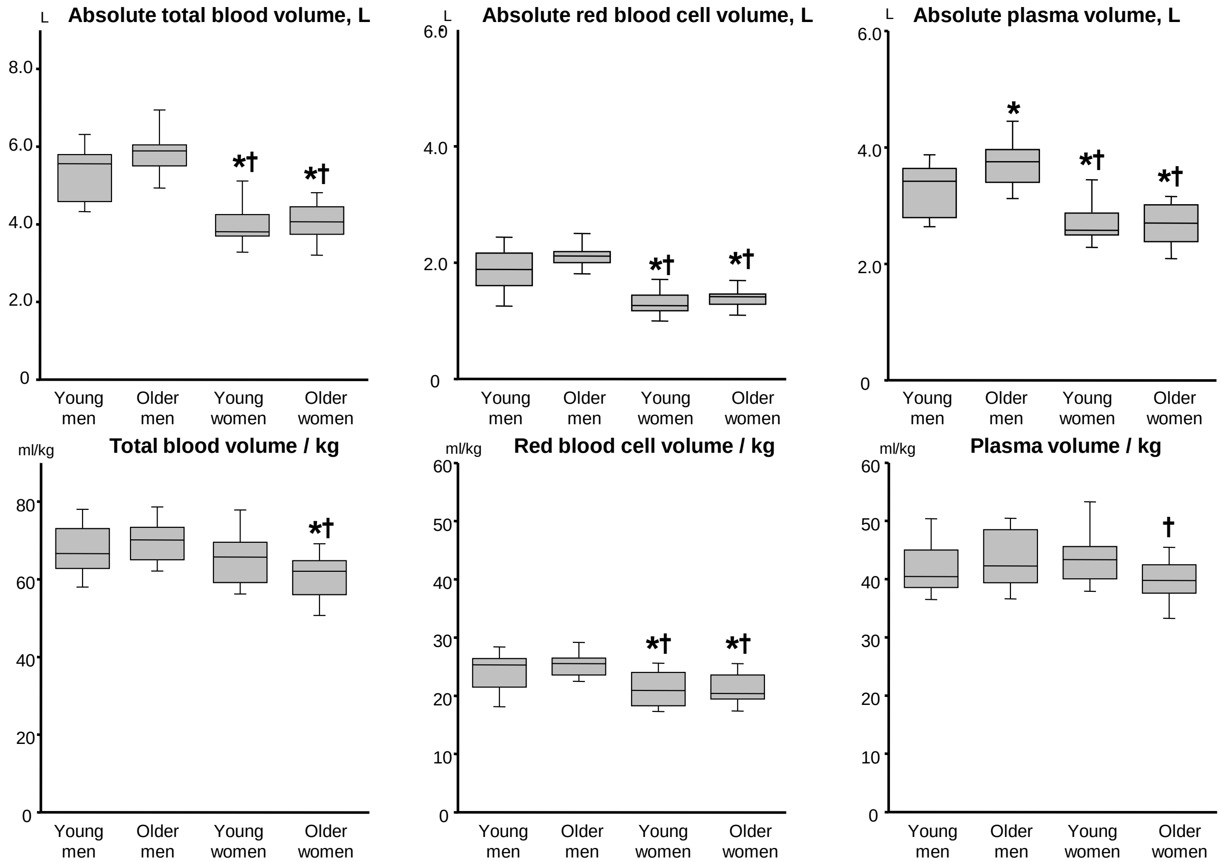
	Infusion < 150 ml/min (n=4)	**Infusion ≥ 150 ml/min** (n=9)	**ANOVA p value**
Infusion rate, ml/min	134 ± 26	191 ± 14	< 0.001
Saline infused during NS1, L	0.88 ± 0.18	0.87 ± 0.10	0.916
Body surface area, m^2	1.72 ± 0.08	1.66 ± 0.13	0.439
Heart rate, beat/min			
Baseline	80 ± 7	84 ± 11	0.514
NS1	90 ± 4*	92± 13*	0.685
Cardiac index (reb), L/m^2			
Baseline	2.84 ± 0.74	3.28 ± 0.65	0.456
NS1	3.61 ± 1.22*	3.99 ± 1.13*	0.514
Mean PCWP, mmHg			
Baseline	10 ± 1	10± 2	0.564
NS1	16 ± 1*	16± 2*	0.618
RAP, mmHg			
Baseline	6 ± 1	6 ± 2	0.624
NS1	10 ± 2*	11 ± 1*	0.229
PCWP/saline slope, $mmHg \cdot L^{-1}$	7 ± 1	7 ± 2	0.965
PCWP/saline slope, $mmHg \cdot L^{-1} \cdot m^2$	12 ± 2	12 ± 3	0.833

Values are mean ± SD. NS1 indicates first session of saline infusion; (reb), by acetylene rebreathing technique; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure. *P < 0.05 vs. baseline.

Supplemental Figure 1

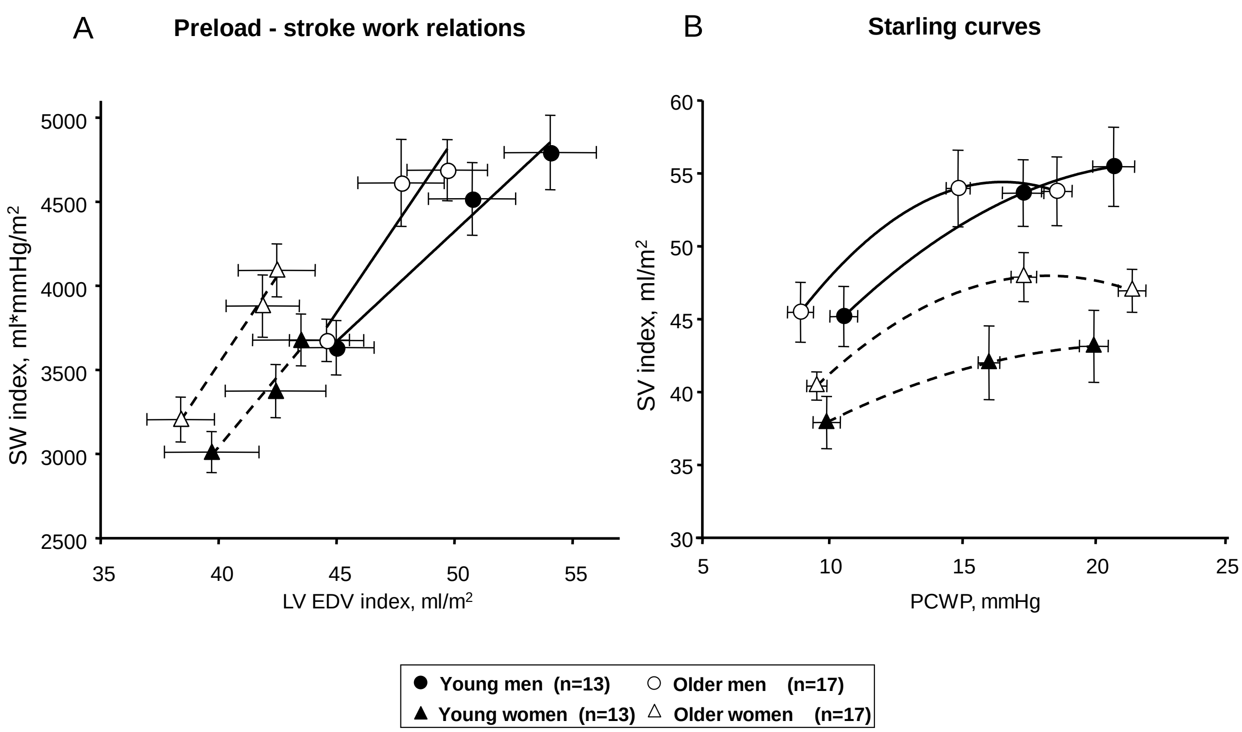


Supplemental Figure 2



***p < 0.05 vs. Young men, and †p < 0.05 vs. Older men.**

Supplemental Figure 3



Supplemental Figure 1

Relationships between baseline PCWP and age, and baseline LVTMP and age in healthy subjects. PCWP indicates pulmonary capillary wedge pressure; LVTMP, left ventricular transmural pressure; ●, healthy men; ○, healthy women.

Supplemental Figure 2

Total blood volume, red blood cell volume, and plasma volume by carbon monoxide rebreathing. *P < 0.05 vs. young men, and †P < 0.05 vs. older men.

Supplemental Figure 3

A. Preload recruitable stroke work

Lines represent linear regressions for young men, (r^2=0.99), older men (r^2=0.96), young women (r^2=0.99) and older women (r^2=0.99). No differences were noted in the slope of preload-stroke work relations among the 4 groups.

B. Frank-Starling relationship

Systolic ventricular performance in healthy subjects. Lines represent results of second linear regression analyses. ● indicates young men; ○, older men; ▲, young women; Δ, older women. Note substantially upward shift of Starling curve in men compared to women.