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RESEARCH ARTICLE

Obesity, venous capacitance, and venous compliance in heart failure with preserved ejection fraction

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Aims Circulating blood volume is functionally divided between the unstressed volume, which fills the vascular space, and stressed blood volume (SBV), which generates vascular wall tension and intravascular pressure. With decreases in venous capacitance, blood functionally shifts to the SBV, increasing central venous pressure and pulmonary venous pressures. Obesity is associated with both elevated venous pressure and heart failure with preserved ejection fraction (HFpEF). To explore the mechanisms underlying this association, we evaluated relationships between blood volume distribution, venous compliance, and body mass in patients with and without HFpEF.

Methods and results Subjects with HFpEF ($n = 62$) and non-cardiac dyspnoea (NCD) ($n = 79$) underwent invasive haemodynamic exercise testing with echocardiography. SBV was estimated (eSBV) from measured haemodynamic variables fit to a comprehensive cardiovascular model. Compared to NCD, patients with HFpEF displayed a leftward-shifted central venous pressure–dimension relationship, indicating reduced venous compliance. eSBV was 81% higher at rest and 69% higher during exercise in HFpEF than NCD (both $P < 0.0001$), indicating reduced venous capacitance. Despite greater augmented eSBV with exercise, the increase in cardiac output was reduced in HFpEF, suggesting operation on the plateau of the Starling curve. Exercise eSBV was directly correlated with higher body mass index ($r = 0.77$, $P < 0.0001$) and inversely correlated with right ventricular–pulmonary arterial coupling ($r = -0.57$, all $P < 0.0001$).

Conclusions Patients with HFpEF display reductions in systemic venous compliance and increased eSBV related to reduced venous capacitance, abnormalities in right ventricular–pulmonary artery interaction, and increased body fat. These data provide new evidence supporting an important role of venous dysfunction in obesity-related HFpEF and suggest that therapies that improve venous function may hold promise to improve clinical status in this cohort.

Keywords Venous function • Venous compliance • Heart failure • Heart failure with preserved ejection fraction • Obesity

Introduction

Over half of all patients with heart failure (HF) have a preserved left ventricular ejection fraction (HFpEF), and up to 80% of these individuals are obese.[1,2] Patients with obesity-related HFpEF display greater volume expansion and more abnormal haemodynamics, but the former cannot fully explain the latter.[3–6] Indeed, many patients with obesity-related HFpEF display normal filling pressures

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at rest that become markedly elevated only during exercise.[7] The mechanisms underlying this behaviour in HFpEF and obesity-related HFpEF remain unclear.

Cardiac filling pressures increase as total blood volume (TBV) increases, but the distribution of blood in the circulation may be even more important. TBV is functionally divided into an unstressed blood volume (UBV) pool, which 'fills' the vascular space just to the point of developing wall tension and intravascular pressure, and the stressed blood volume (SBV) pool, which is the volume of blood in excess of UBV that increases wall tension and contributes to pressure throughout the vascular system. The distribution between SBV and UBV is regulated by the autonomic nervous system. Sympathetic outflow causes venoconstriction that acutely mobilizes blood from the hepatosplanchnic venous reservoir, reducing systemic venous capacitance to increase SBV, shifting blood to the central circulation.

Central venous pressure (CVP) accordingly increases as SBV rises, but CVP is also influenced by the compliance properties of the central veins and the ability of the right heart to discharge blood and perfuse the lungs, measures that are frequently impaired in patients with obesity, along with increases in sympathetic tone.[3,8,9] Accordingly, we hypothesized that patients with HFpEF, particularly obesity-related HFpEF, would display greater increases in SBV at rest and during exercise, and that this would be related to reductions in central venous compliance, abnormalities in right ventricular–pulmonary arterial (RV-PA) coupling, and increases in body fat.

Methods

Study population

Consecutive patients undergoing invasive haemodynamic exercise testing for the evaluation of unexplained dyspnoea at the Mayo Clinic, Rochester, MN, between February 2018 and January 2020 were prospectively enrolled in this study. HFpEF was defined according to current guidelines as patients with functional class II–III dyspnoea, ejection fraction ≥50%, and elevated pulmonary capillary wedge pressure (PCWP, >15 mmHg at rest and/or ≥25 mmHg with exercise) in the absence of ischaemia, valvular heart disease, cardiomyopathy, pericardial disease, high output failure, or clinically significant lung disease.[10] Control subjects with non-cardiac dyspnoea (NCD) were defined as patients with exertional dyspnoea but no evidence of HF or cardiac pathology to account for their symptoms (normal rest and exercise PCWP). NCD were identified from the same series of patients and also from an earlier series of patients who underwent the same evaluation with all necessary data (online supplementary *Figure S1*). Non-obese HFpEF was defined by body mass index (BMI) <30 kg/m^2, and obese HFpEF was defined by BMI ≥30 kg/m^2. The Mayo Clinic Institutional Review Board approved the study, and written informed consent was prospectively provided by all subjects.

Haemodynamic assessment

Subjects underwent symptom-limited supine cycle ergometry with simultaneous expired gas analysis as previously described.[11–14] Right atrial pressure or CVP, pulmonary artery (PA) pressures, and PCWP were measured visually at end expiration taking the mean of ≥3 beats on distinct respiratory cycles using 2 Fr high fidelity micromanometer-tipped catheters. A 4–6 Fr radial arterial cannula was used to measure arterial blood pressure and sample arterial blood gases. Arterio-venous oxygen difference (AVO_2 diff) was directly measured as the difference between systemic arterial and PA oxygen contents. Oxygen consumption (VO_2) was measured using expired gas analysis (MedGraphics, St. Paul, MN, USA), with values taken as the mean for a 30 s interval preceding arterial and venous blood sampling in each phase. Cardiac output (CO) was then calculated using the direct Fick method (CO = VO_2/AVO_2 diff).

After baseline data were acquired, haemodynamic assessment and expired gas analysis were performed during supine cycle ergometry exercise, starting at 20 W for 5 min (60 rpm), increasing 20 W increments in 3 min stages to volitional exhaustion.

Estimation of stressed blood volume

Venous capacitance refers to the volume of blood contained in the venous circulation at a given pressure. The blood volume required to simply fill the vascular space to the point of just starting to develop wall tension is defined as the UBV. UBV normally constitutes approximately 70–75% of TBV. The volume of blood that distends the vessel walls in excess of the UBV to drive elevation in pressure is termed SBV (normally 25–30% of TBV). As veins contract, as with sympathetic activation, venous capacitance decreases, increasing SBV and decreasing UBV.

Direct measurements of UBV and SBV require complex experimental preparations and maneuvers that are not readily applicable to humans, and certainly not to exercise physiology studies. The principles of estimating SBV based on measurements of CO, CVP and PCWP have been detailed previously (online supplementary *Methods S1*).[15,16] In the present study, SBV was estimated based on a more general approach that uses a cardiovascular model in combination with a parameter optimization algorithm (online supplementary *Methods S1*). In brief, invasive measured values of CO, CVP, PCWP, arterial pressure, PA pressure, are used along with echocardiographic left ventricular ejection fraction as inputs to the model. The algorithm performs an unbiased search of the multidimensional space comprised of the model's parameters to optimize the concordance between all of the measured haemodynamic parameters to model outputs. This algorithm has been implemented in a real-time simulation (retrieved online from URL: http://harvi.online; access date: 17 February 2020) that has been used in prior studies.[16,17] Estimated SBV (eSBV) is one of the key outputs of the model and is the only parameter from the model used in the present analysis. Estimated UBV is then calculated from TBV−eSBV. For the purposes of this analysis, it was assumed that the change in TBV during exercise was negligible, so increases in SBV would be counterbalanced 1:1 by reductions in UBV, reflecting a decrease in venous capacitance.

Plasma volume (PV) was calculated using a regression formula that has been validated against radiolabelled indicator dilution studies in both patients with HF and in NCD, wherein PV = (1-haematocrit) × (a + [b × weight in kg]), where a = 1530 for men and 864 for women and b = 41 for men and 47.9 for women.[18] TBV is then calculated as PV/(1-haematocrit).[19]

Assessment of venous compliance and ventricular function

Two-dimensional, M-mode, Doppler, and tissue Doppler echocardiography was performed by experienced sonographers according to

the American Society of Echocardiography guidelines and interpreted offline by an experienced investigator in a blinded fashion.[20] To evaluate central venous stiffness properties, CVP was plotted as a function of inferior vena cava (IVC) dimension measured simultaneously at the time of catheterization in HFpEF and NCD patients at rest. Total epicardial volume was estimated from two hemi-ellipsoids containing both atria and ventricles with the apical four-chamber view.[3] Ventricular interdependence was quantified in the parasternal short-axis view on two-dimensional echocardiography by the left ventricular eccentricity index.[3] Epicardial fat thickness was measured on the free wall of the right ventricle at end systole.[6]

Focused evaluation of left and right ventricular systolic function was performed simultaneously with invasive assessment at rest and during all stages of exercise. Left ventricular ejection fraction was determined using Simpson's biplane method of disks. Right ventricular function was assessed by tricuspid valvular s′ velocity (TV s′) (online supplementary *Figure S2*). RV-PA coupling was assessed by the ratio of TV s′ to directly measured PA pressure.[12]

Statistical analysis

Data are presented as mean ± standard deviation, median [interquartile range (IQR)], or number (%). Between-group differences were compared using the unpaired *t*-test, Wilcoxon rank-sum test, χ^2 or Fisher's exact test as appropriate. Correlation analyses were used to assess relationships with eSBV. Multivariable regression analyses were used to determine the difference in the intercepts of the relationship of eSBV with BMI between NCD and HFpEF groups. Because patients with HFpEF are typically older and heavier than NCD, we also performed a sensitivity analysis where HFpEF and NCD were frequency matched by age, sex, and BMI ($n = 49$ NCD and $n = 49$ HFpEF). A two-sided *P*-value of <0.05 was considered statistically significant. All data were analysed using JMP14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Subject characteristics and haemodynamics

Compared with NCD, subjects with HFpEF were older, more obese and anaemic, and displayed significantly higher N-terminal pro brain natriuretic peptide levels (*Table 1*). The prevalence of atrial fibrillation and diuretic use was greater in HFpEF compared to NCD. Subjects with HFpEF displayed lower mitral e′ velocity, higher E/e′ ratio, and greater right ventricular size compared with NCD.

Rest and exercise haemodynamics

Compared with NCD, HFpEF subjects displayed higher CVP, PA pressures and PCWP, at rest and during exercise (*Table 2*). CO and VO_2 were similar in HFpEF and NCD at rest, but were both reduced in HFpEF as compared to NCD during exercise.

Central venous pressure–dimension relationships

Inferior vena cava dimension increased with higher CVP in both groups, but CVP was higher for any IVC dimension in HFpEF, with a steeper slope of increase in CVP for any given increase in IVC dimension in HFpEF, indicating reduced systemic venous compliance (increased local venous stiffness) at rest (*Figure 1A*).

Distribution of blood volume in heart failure with preserved ejection fraction and non-cardiac dyspnoea

Total blood volume and plasma volume were 11% and 14% greater in HFpEF than NCD (both $P < 0.005$; *Table 1*). In contrast, eSBV was 81% higher in HFpEF vs. NCD at rest [2494 mL (IQR 1691–3114) vs.1375 mL (IQR 1080–1821)] (*Table 3*). The higher eSBV was not ascribable to the modest elevation in TBV in HFpEF, as the ratio of eSBV to TBV in subjects with HFpEF was nearly 50% greater than that observed in NCD (44% vs. 30%, $P < 0.0001$; *Table 3*, *Figure 1B*).

Compared with rest, eSBV increased acutely during exercise in both HFpEF and NCD. The absolute eSBV change from baseline was higher in the HFpEF group than in NCD (*Table 3*, *Figure 1C*), but the percent change from baseline was not different between groups [49% vs. 53% at 20 W exercise ($P = 0.7$), 55% vs. 58% at peak exercise ($P = 0.8$)]. Higher eSBV during exercise was associated with lower peak VO_2 ($r = -0.4$, $P < 0.0001$).

The ratio of eSBV to TBV increased in a linear fashion with increases in BMI among both NCD and HFpEF patients, but was consistently higher in HFpEF even after accounting for the impact of BMI (*Figure 2*) or body weight (online supplementary *Figure S3*). In both NCD and HFpEF, PCWP was correlated with SBV at rest as well as during exercise (online supplementary *Tables S1* and *S2*, *Figure S4A*, *C*).

At the same level of SBV, HFpEF patients displayed higher PCWP. On the contrary, at the same level of SBV, HFpEF displayed lower CO compared to NCD (online supplementary *Figure S4B*,*D*). Moreover, despite the higher CVP and eSBV in HFpEF, increases in CO, and the increase in CO relative to the change in eSBV with exercise were all significantly reduced as compared to NCD (*Figure 3*). This suggests that patients with HFpEF were operating on the plateau of the Starling curve (*Figure 4*).

Stressed blood volume, body mass, and right ventricular–pulmonary arterial coupling

Estimated SBV during exercise was directly correlated with general adiposity measured as BMI ($r = 0.77$, $P < 0.0001$; *Figure 5A*). Exercise eSBV also increased with greater impairments in RV-PA coupling (ratio of TV s′ to PA pressure, $r = -0.57$, $P < 0.0001$; *Figure 5B*).

As compared to non-obese HFpEF, subjects with obese HFpEF were younger, with higher TBV, and higher PCWP during exercise (online supplementary *Tables S3* and *S4*). Epicardial volume, epicardial fat thickness, and measure of ventricular interdependence were increased in obese HFpEF (online supplementary *Table S3*). Increases in SBV appeared to play a greater role in obesity-related HFpEF than in non-obese HFpEF: eSBV was 64% higher in obese HFpEF at rest [2860 mL (IQR 2096–3470) vs.1749 mL (IQR

Table 1 Baseline characteristics, cardiac structure and function

	NCD ($n = 79$)	HFpEF ($n = 62$)	*P*-value
Age (years)	61 ± 11	68 ± 12	0.0005
Female sex, *n* (%)	39 (49)	40 (65)	0.06
Body mass index (kg/m^2)	28.1 ± 5.5	33.3 ± 6.9	<0.0001
Obesity (BMI ≥ 30 kg/m^2), *n* (%)	27 (35)	42 (68)	<0.0001
Estimated plasma volume (mL)	2903 ± 587	3304 ± 708	0.0007
Estimated total blood volume (mL)	4889 ± 930	5413 ± 1025	0.002
H_2FPEF score	2 (1–4)	4 (3–6)	<0.0001
HFA-PEFF score	1 (0–2)	3 (2–5)	<0.0001
Comorbidities, *n* (%)			
Hypertension	49 (63)	47 (76)	0.1
Coronary artery disease	15 (20)	13 (21)	0.9
Atrial fibrillation	7 (9)	21 (34)	0.0002
Diabetes mellitus	10 (13)	14 (23)	0.1
COPD	4 (5)	8 (13)	0.1
Medications, *n* (%)			
ACEI or ARB	21 (27)	20 (32)	0.5
Beta-blocker	27 (34)	29 (47)	0.2
Diuretics	17 (22)	34 (55)	<0.0001
Calcium channel blocker	16 (22)	14 (23)	0.9
Laboratories			
Haemoglobin (g/dL)	13.5 ± 1.6	12.8 ± 1.8	0.03
Creatinine (mg/dL)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.1
NT-proBNP (pg/mL)	71 (39–177)	217 (93–502)	0.0006
Cardiac structure and function			
Left ventricular			
LV diastolic dimension (mm)	48 ± 5	49 ± 5	0.6
LV mass index (g/m^2)	85 ± 22	85 ± 19	0.9
LV end-diastolic volume (mL)	98 ± 34	105 ± 35	0.3
LV end-systolic volume (mL)	37 ± 16	40 ± 13	0.4
LV ejection fraction (%)	62 ± 7	61 ± 6	0.4
Mitral septal e′ velocity (cm/s)	8.1 ± 2.1	7.1 ± 2.0	0.006
E/e′ ratio	8.3 (6.5–10.0)	11.4 (8.9–15.7)	<0.0001
LA volume index (mL/m^2)	29 (25–32)	34 (25–41)	0.1
Right ventricular			
Estimated RVSP (mmHg)	30 ± 8	43 ± 21	<0.0001
RV basal dimension (mm)	34 ± 7	40 ± 7	<0.0001
RV mid cavity dimension (mm)	28 ± 7	32 ± 6	0.0004
RV longitudinal dimension (mm)	69 ± 9	74 ± 9	0.0007
Central venous			
Maximal IVC dimension (mm)	14 ± 5	17 ± 6	0.009
Minimal IVC dimension (mm)	6 ± 4	12 ± 7	<0.0001
Pericardial and ventricular interaction			
Total epicardial volume (mL)	637 (530–781)	723 (586–781)	0.02
EAT thickness (mm)	3 (1–5)	5 (3–5)	0.0003
Eccentricity index at end-diastole	0.97 ± 0.09	1.02 ± 0.10	0.006
Eccentricity index at end-systole	0.96 ± 0.10	1.02 ± 0.12	0.01

Values are mean ± standard deviation, *n* (%), or median (interquartile range).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; EAT, epicardial adipose tissue; HFpEF, heart failure with preserved ejection fraction; IVC inferior vena cava; LA, left atrial; LV, left ventricular; NCD, non-cardiac dyspnoea; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular; RVSP, right ventricular systolic pressure.

Table 2 Haemodynamics at rest and during exercise between heart failure with preserved ejection fraction and non-cardiac dyspnoea

	Baseline		20 W exercise		Peak exercise	
	NCD ($n = 79$)	HFpEF ($n = 62$)	NCD ($n = 79$)	HFpEF ($n = 62$)	NCD ($n = 79$)	HFpEF ($n = 62$)
Peak workload (W)	–	–	–	–	72 ± 33	57 ± 33*
Vital signs						
Heart rate (bpm)	68 ± 12	71 ± 12	90 ± 14	93 ± 15	116 ± 23	102 ± 22*
Systolic blood pressure (mmHg)	145 ± 23	153 ± 25**	168 ± 28	179 ± 33**	185 ± 31	184 ± 40
Central pressures						
CVP (mmHg)	5 (3–6)	10 (8–13)***	8 (6–10)	16 (13–24)***	8 (6–10)	18 (14–24)***
PA systolic pressure (mmHg)	27 (24–31)	38 (32–49)***	40 (32–44)	56 (51–67)***	43 (35–50)	64 (52–76)***
PA mean pressure (mmHg)	17 (14–19)	25 (21–31)***	26 (23–29)	42 (35–52)***	28 (23–31)	45 (40–53)***
PCWP (mmHg)	8 (6–10)	16 (13–20)***	14 (12–17)	27 (23–33)***	15 (12–18)	28 (25–35)***
Oxygen delivery						
Cardiac output (L/min)	5.4 ± 1.6	5.5 ± 1.9	8.3 ± 2.3	7.6 ± 2.4	10.7 ± 3.1	9.2 ± 3.3*
Oxygen consumption (mL/kg/min)	2.7 ± 0.6	2.5 ± 0.6	7.9 ± 2.3	7.2 ± 1.7**	13.4 ± 4.3	10.1 ± 4.3***
Ventilatory performance						
V_E (L/min)	7.0 ± 2.0	7.6 ± 2.3	18.7 ± 8.5	17.4 ± 8.6	37.9 ± 10.2	33.0 ± 12.7**
V_T (mL)	524 ± 189	536 ± 195	840 ± 194	724 ± 315***	1291 ± 370	1092 ± 444**
V_E/VCO_2 ratio	38 ± 5	38 ± 6	32 ± 6	36 ± 6*	33 ± 6	35 ± 5
V_D/V_T ratio	0.40 ± 0.07	0.42 ± 0.09	0.31 ± 0.06	0.37 ± 0.08*	0.25 ± 0.07	0.33 ± 0.11***
RER	0.80 ± 0.09	0.81 ± 0.09	0.87 ± 0.12	0.88 ± 0.15	1.05 ± 0.12	1.02 ± 0.13
Cardiac function						
LV ejection fraction (%)	61 ± 8	61 ± 8	63 ± 9	66 ± 8	64 ± 8	69 ± 8**
TV s′ (cm/s) ($n = 32/43$)	11.5 ± 2.5	9.9 ± 2.3*	13.9 ± 3.1	10.7 ± 2.6***	15.6 ± 3.9	11.5 ± 3.3***

Values are mean ± standard deviation, or median (interquartile range).
CVP, central venous pressure; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular; NCD, non-cardiac dyspnoea, PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RER, respiratory exchange ratio; TV, tricuspid valve; VCO_2, carbon dioxide volume; V_D, pulmonary dead space; V_E, minute ventilation; V_T, tidal volume.
*$P < 0.01$ vs. NCD.
**$P < 0.05$ vs. NCD.
***$P < 0.001$ vs. NCD.

1460–2470)] and remained higher during exercise (online supplementary *Table S5*).

Sensitivity analyses

Given the baseline differences in age, sex and BMI between HFpEF and NCD, a separate sensitivity analysis was performed in a smaller sub-cohort of patients ($n = 49/49$) matching for these three covariates (online supplementary *Tables S6–S8*). All group differences in eSBV dynamics were similar in this matched sensitivity analysis (online supplementary *Figures S5* and *S6*).

To complement the primary analysis using the non-linear pressure–volume relationship, eSBV was also calculated using a linear vascular pressure–volume relationships model (online supplementary *Tables S9* and *S10*). In this model, eSBV dynamics showed similar group differences as observed for the non-linear vascular pressure–volume relationships.

Discussion

In this study, we aimed to better understand the role of the venous circulation in HFpEF, particularly in patients with the obese phenotype of HFpEF. To do this we compared CVP in relation to simultaneously measured IVC dimension, and evaluated the functional distribution of blood volume in the vascular space between stressed and unstressed components at rest and during exercise. We found that (i) the pressure–dimension relationship in the IVC was shifted upward in HFpEF, and the increase in CVP with any increase in IVC dimension was steeper, identifying a reduction in systemic venous compliance; (ii) eSBV was greater in subjects with HFpEF compared to NCD during rest and exercise, and the ratio of eSBV to TBV was greater, implying an abnormality in systemic venous capacitance; (iii) despite greater augmentation in eSBV to facilitate venous return, patients with HFpEF displayed impaired ability to augment CO during exercise, suggesting that HFpEF patients were operating on the plateau of the Starling curve; (iv) eSBV increased as RV-PA coupling became more impaired; and (v) eSBV was strongly related to body mass and was significantly higher in obese compared to non-obese HFpEF even after accounting for their greater TBV. These findings provide new insights into the potential mechanistic links between abnormalities in venous compliance, venous capacitance, RV-PA coupling, obesity, and HFpEF. The present data also suggest that therapies targeting venous

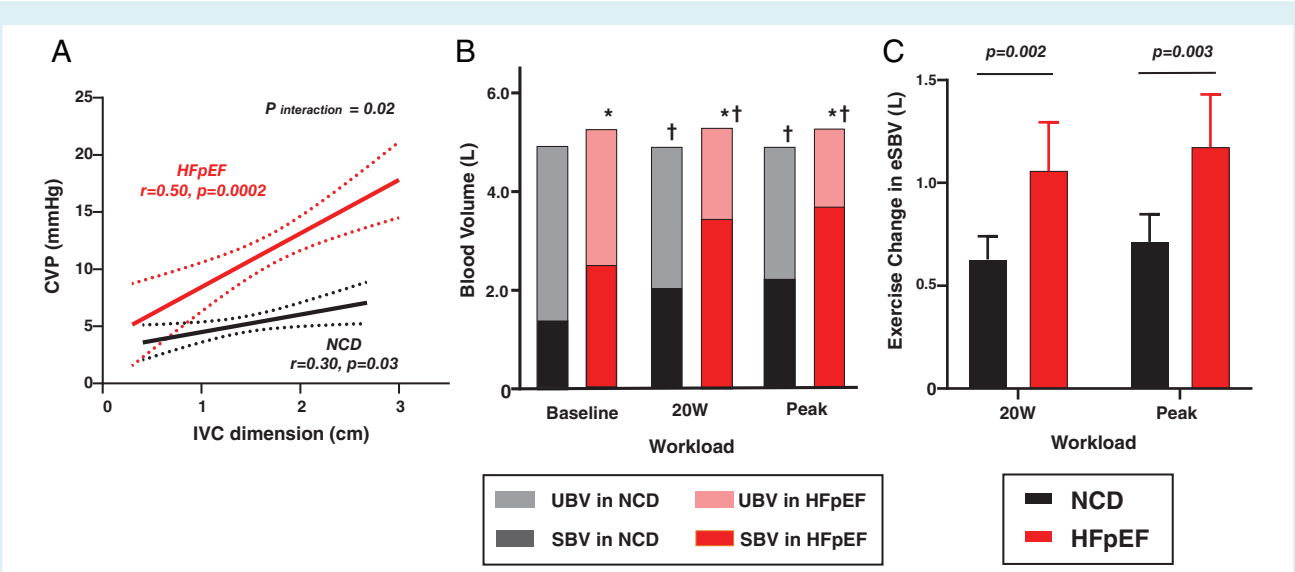

Figure 1 In both non-cardiac dyspnoea (NCD) and heart failure with preserved ejection fraction (HFpEF), central venous pressure (CVP) increased with increases in inferior vena cava (IVC) dimension, but CVP was higher for any given IVC dimension, and increased more strikingly with further increases in dimension in HFpEF *(A)*. Stressed blood volume (SBV) was greater in HFpEF patients compared with NCD at rest and during exercise. SBV increased significantly with exercise in both groups *(B)*. The absolute SBV change with exercise from baseline was greater in the HFpEF group compared with NCD *(C)*. eSBV, estimated stressed blood volume; UBV, unstressed blood volume. $^{\dagger}P < 0.05$ vs. baseline in SBV. $^{*}P < 0.05$ vs. NCD in SBV.

Table 3 Distribution of blood volume at rest and during exercise

	NCD ($n = 79$)	HFpEF ($n = 62$)	*P*-value
Baseline stressed volume (mL)	1375 (1080–1821)	2494 (1691–3114)	<0.0001
20 W stressed volume (mL)	2051 (1519–2686)	3504 (2808–4434)	<0.0001
Peak stressed volume (mL)	2250 (1713–2652)	3795 (2878–4376)	<0.0001
Baseline stressed volume/BW (mL/kg)	17 ± 4	27 ± 8	<0.0001
20 W stressed volume/BW (mL/kg)	25 ± 6	38 ± 6	<0.0001
Peak stressed volume/BW (mL/kg)	26 ± 7	39 ± 6	<0.0001
Change 20 W from baseline (mL)	636 ± 514	1076 ± 926	0.002
Change peak from baseline (mL)	722 ± 608	1181 ± 1010	0.003
%Change 20 W from baseline (%)	49 ± 46	53 ± 49	0.7
%Change peak from baseline (%)	55 ± 55	58 ± 55	0.8
Baseline stressed volume/TBV (%)	30 (24–34)	44 (35–57)	<0.0001
20 W stressed volume/TBV (%)	43 (36–49)	65 (57–76)	<0.0001
Peak stressed volume/TBV (%)	46 (37–50)	69 (57–77)	<0.0001
Baseline unstressed volume (mL)	3532 (2999–3783)	2910 (2177–3431)	<0.0001
20 W unstressed volume (mL)	2736 (2520–3078)	1752 (1529–2246)	<0.0001
Peak unstressed volume (mL)	2692 (2346–3021)	1607 (1292–2094)	<0.0001

Values are mean ± standard deviation, or median (interquartile range).
BW, body weight; TBV, total blood volume.

properties may be effective to improve clinical status in patients with HFpEF.

Venous function and blood volume distribution

The majority of blood volume in man resides in veins, yet the relations of SBV to venous function and central haemodynamics remain little studied in HF.[21] During physical activity, venous return to the heart is enhanced through the combined pumping actions of skeletal muscle aided by venoconstriction in the large capacitance veins of the abdomen, which serve to translocate blood from the abdominal venous reservoir to the heart and lungs.[22–24] Patients with HFpEF develop marked elevation of biventricular filling pressures during activity leading to pulmonary congestion.[11–14,25] This

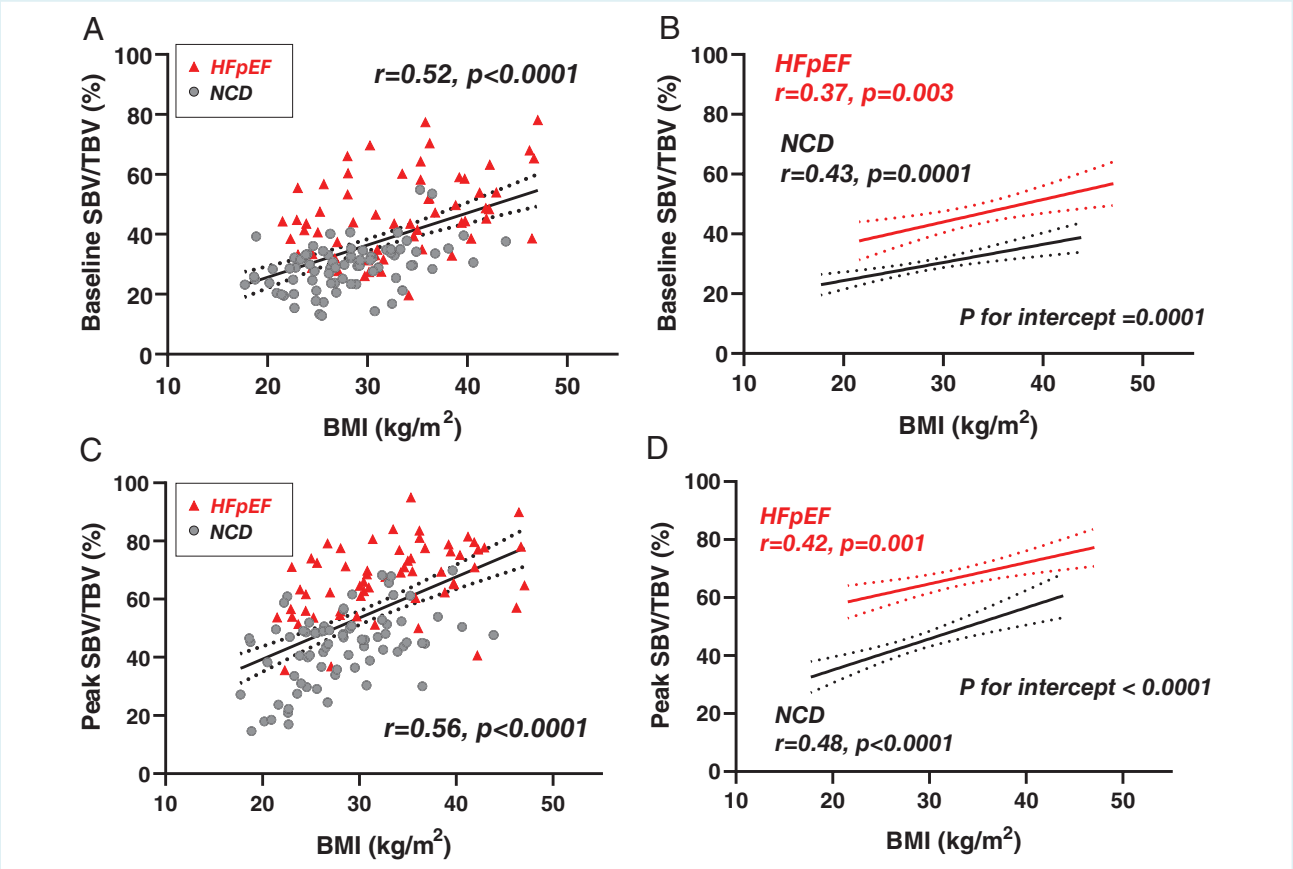

Figure 2 The ratio of stressed blood volume (SBV) to total blood volume (TBV) increased with higher body mass index (BMI) among both non-cardiac dyspnoea (NCD) and heart failure with preserved ejection fraction (HFpEF) at rest *(A)* as well as during exercise *(C)*. At the same level of BMI, HFpEF patients displayed higher SBV relative to TBV compared with NCD (*B*, *D*).

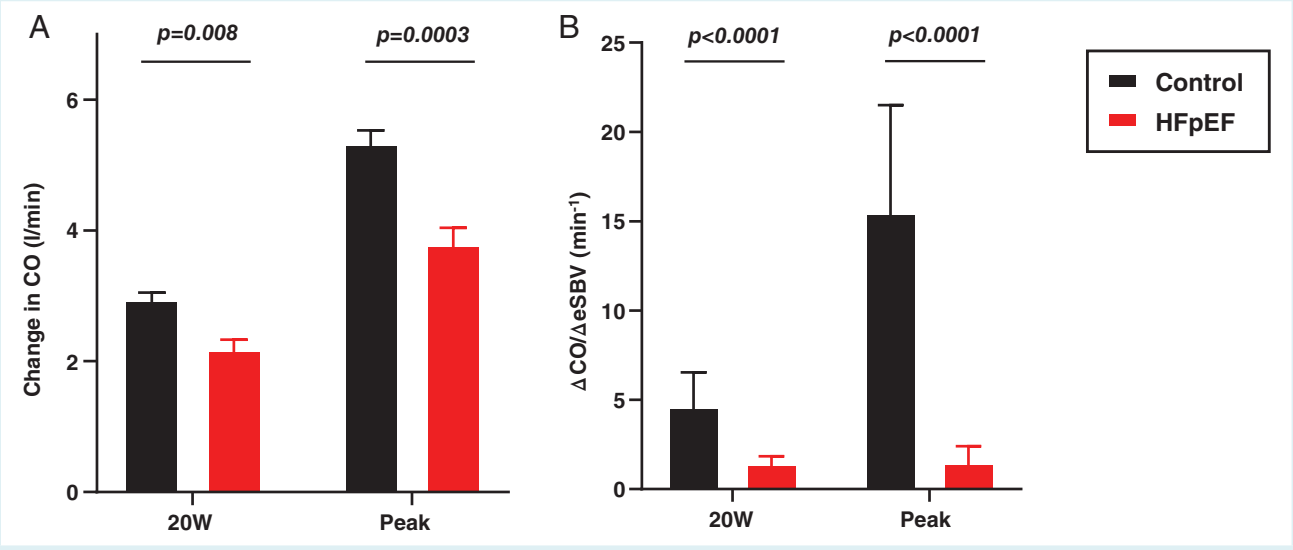

Figure 3 Changes in cardiac output (CO) with exercise from baseline were lower in the heart failure with preserved ejection fraction (HFpEF) group compared with non-cardiac dyspnoea (NCD) *(A)*. The ratio of change in CO to the change in stressed blood volume was lower in HFpEF compared with NCD *(B)*. eSBV, estimated stressed blood volume.

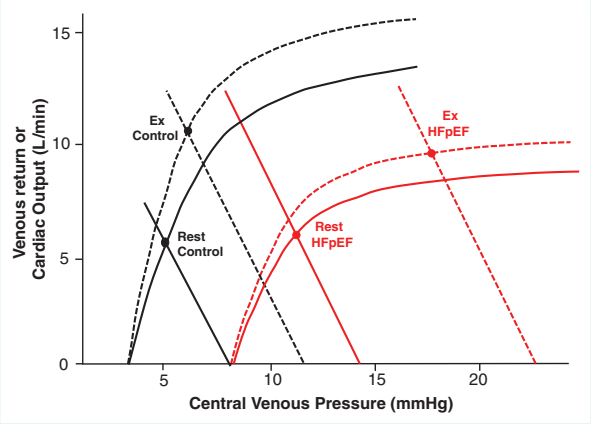

Figure 4 Venous return and Frank–Starling curves at rest and during exercise (Ex). Group mean values for controls (black) and heart failure with preserved ejection fraction (HFpEF, red, error bars not shown for clarity) for central venous pressure (CVP) and cardiac output (CO). The diagonal straight lines represent venous return curves, which intersect with the Frank–Starling curves (rectangular hyperbolas) at the coordinates of CVP and CO (which is equal to venous return at steady state). The X intercept of the venous return curve represents mean systemic filling pressure, which increases with higher stressed blood volume (SBV). In controls, venous capacitance is high, meaning that most of blood volume resides in the unstressed blood volume (UBV) compartment and SBV is low. During exercise (dashed lines), the venous return curve shifts rightward as venous capacitance decreases, leading to an increase in SBV and mean systemic filling pressure. This increases venous return and is accompanied by a nearly 50% increase in cardiac output with only mild increase in CVP in controls, because the Starling curve also shifts up to the left due to enhanced inotropy, chronotropy, and vasodilatation. In HFpEF, venous capacitance is reduced shifting blood from the UBV to the SBV, increasing mean systemic filling pressure, reflected by a rightward shift in the venous return curve at rest. During exercise, there is a greater increase in SBV in HFpEF patients, resulting in a greater rightward shift in the venous return curve. The fact that CO increases minimally with respect to the increase in CVP, as shown above, and relative to SBV, as shown in *Figure 5*, suggests that the heart is operating on the plateau of the Starling curve, where further increases in CO are not achieved with venoconstriction.

elevation in filling pressures is most often related to cardiac abnormalities alone, but alterations in systemic venous properties may also contribute.

Total blood volume can be divided functionally into the UBV and SBV components.[24] The UBV refers to the volume of blood necessary to essentially fill the vascular space. SBV represents the additional blood volume beyond UBV that increases wall tension in the venous vasculature and is a major determinant of right- and left-sided ventricular filling pressures. In this way, SBV is an important determinant of CO. SBV normally accounts for approximately 25–30% of the TBV.[24,26] The present data were consistent with this, with an average eSBV at rest of 30% in NCD.

In contrast, eSBV accounted for a higher proportion (44%) in patients with HFpEF, which was an even higher volume given that TBV was also modestly increased. The distribution of SBV and UBV is tightly regulated by the autonomic nervous system. With acute increases in sympathetic discharge, the capacity of the splanchnic veins decreases, creating a functional shift of blood from the UBV to the SBV, allowing for recruitment of preload into the central circulation. Thus, the increases in SBV and the greater ratio of SBV to TBV provide direct evidence for a decrease in venous capacitance in patients with HFpEF. Obesity is strongly associated with heightened sympathetic tone,[9] leading to our hypothesis that venous capacitance would be even more impaired in obese HFpEF. The experimental data confirmed this hypothesis, but also demonstrate that SBV was higher in HFpEF even after accounting for the effects of greater body fat (*Figure 2*).

Determinants of increased stressed blood volume

Hypervolaemia contributes to abnormal haemodynamics in HFpEF, but the current study shows that the distribution of blood volume may be even more important (*Figure 1B*). The proportional increase in SBV during exercise was similar in cases and NCD, but because the absolute SBV was higher at rest in HFpEF, the absolute increase with stress was also greater in HFpEF, especially obese HFpEF. This finding, in tandem with the higher CVP relative to IVC dimension observed (*Figure 1A*), provides new evidence of venous dysfunction in patients with HFpEF, mirroring the previously described increases in arterial stiffness in this syndrome.[1,2,27]

Despite the greater increase in SBV during exercise in HFpEF, the rate of increase in CO was significantly lower compared to NCD (*Figure 3A*). In healthy adults, increased venous return caused by SBV recruitment during exertion results in an increased CO through the Frank–Starling mechanism. However, in HFpEF, the increase of CO was impaired, despite a greater driving force for venous return (i.e. SBV) (*Figure 3B*). This suggests that HFpEF patients were more likely to be operating on the plateau of the Starling curve, where increases in venous return curves cannot be translated to increases in forward flow (*Figure 4*).

Central venous pressure increases from venoconstriction (increased SBV), but this increased venous blood must also be drained from a functional right heart-PA dyad. In this regard, we further observed that impairments in RV-PA coupling during exercise were associated with greater increases in eSBV. Thus the present data reveal how patients with the obese phenotype of HFpEF are uniquely positioned to experience abnormal haemodynamics with exertion, through the synergistic combination of an excessively-loaded heart due to reductions in venous compliance and capacitance and inadequate ability of the heart to distribute this increase in venous return to the body, resulting in dramatic increases in PCWP and CVP during exercise.

Impact of body composition

Obesity has emerged as one of the most important risk factors for HFpEF. Patients with the obese phenotype of HFpEF display some

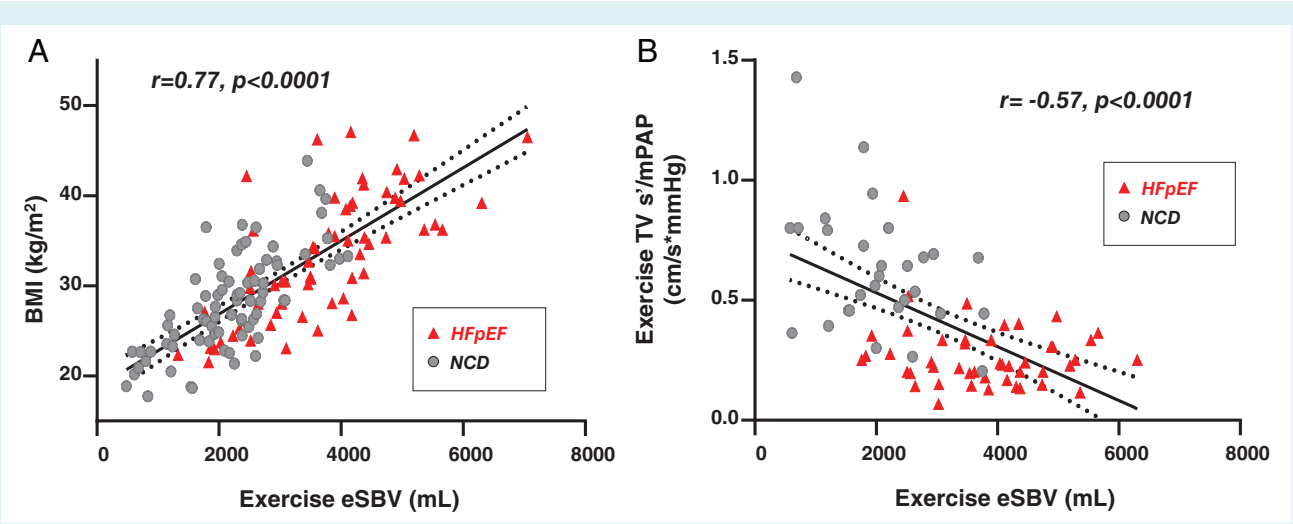

Figure 5 Stressed blood volume estimated by the non-linear model at peak exercise was strongly correlated with body mass index (BMI) *(A)* and right ventricular–pulmonary arterial coupling assessed by tricuspid valvular s′ velocity/mean pulmonary artery pressure (TV s′/mPAP) *(B)*. eSBV, estimated stressed blood volume; HFpEF, heart failure with preserved ejection fraction; NCD, non-cardiac dyspnoea.

features that are distinct from non-obese HFpEF, including greater overall plasma volume expansion, more cardiac remodelling, more adverse RV-PA interaction, and enhanced pericardial restraint.[3–6,19] Visceral adiposity in particular has recently emerged as a key risk factor and potential mediator.[6,28,29] Obese individuals display structural and functional vascular abnormalities resulting in reduced venous distensibility that may contribute to a higher SBV.[8] There may also be direct mechanical effects related to visceral fat raising intra-abdominal pressure.[29] As intra-abdominal pressure rises due to increase visceral adipose tissue, a higher intraluminal pressure is required to maintain adequate transmural distending pressure. An ostensible requirement for higher SBV in the obese phenotype of HFpEF to maintain perfusion may explain why these patients are more likely to display worsening kidney function during diuresis at the time of hospitalization,[5] despite greater TBV.[19] Measures of ventricular interdependence were increased in obese HFpEF. This may render obese patients more vulnerable to the deleterious effects of increased SBV because any elevation in CVP will lead to greater left atrial hypertension due to increased coupling between the right and left heart. Finally, excess body fat is associated with deranged autonomic balance, and this has also been demonstrated in HFpEF where arterial baroreflex sensitivity has been shown to be impaired.[30]

Clinical implications

Fudim and colleagues have recently shown in a series of elegant studies that acute, transient splanchnic nerve block can reduce cardiac filling pressures in patients with HF and reduced ejection fraction, an effect almost certainly mediated by a decrease in SBV.[31–33] In addition to neural modulation, it is possible that pharmacologic therapies could attain similar effects by reducing venous tone or improving venous compliance properties. In addition to calling for new studies into therapies targeting venous function, the results of the present study also provide additional rationale to support weight loss as a means to treat HFpEF.[34] Indeed, prior studies in patients without HF have demonstrated substantial reductions in CVP following various weight loss interventions.[35] The present data suggest a novel mechanism by which weight loss may improve haemodynamics.

Limitations

The primary limitation of this study lies in the fact that SBV was not directly measured but estimated using validated formulas. The analytical approach employed to estimate SBV (online supplementary *Figure S7-S9*) has been validated in animals and provides the theoretical framework for understanding the fundamental relationships between pressures, CO and SBV. Furthermore, the complexities of experimental methods required to actually measure SBV make them inapplicable to studying changes of SBV during exercise in humans. PV and TBV were also estimated using a separate method, and not directly measured. If the regression formulas differed in cases and NCD this could bias the estimates of plasma and blood volume. To simplify the analysis, we ignored the effect of haemoconcentration during exercise, which slightly decreases TBV. However, there was no significant difference between HFpEF and NCD, indicating that this assumption did not introduce meaningful bias. Right ventricular s′ velocity could not be measured during exercise in several participants, but baseline characteristics did not differ in those with and without adequate imaging windows (online supplementary *Table S11*). The present data originate from a single, tertiary referral center and as such is subject to selection and referral bias. The cross-sectional design limits the ability to address causality. Future studies testing interventions targeted to SBV will be necessary to more thoroughly evaluate causality and explore mechanisms.

Conclusions

Patients with HFpEF display higher venous pressure relative to caval dimension, and increased SBV at rest and during exercise, indicating abnormalities in venous compliance and capacitance, respectively. Despite the higher venous pressure, CO reserve is impaired, further contributing to marked central congestion in the heart and lungs. Elevation in SBV is directly correlated with abnormalities of RV-PA interaction and with measures of adipose tissue accumulation. These data provide new insights into the complex relationships between venous function, obesity, and HFpEF. Further study is indicated to explore therapies targeting venous function as a means to improve symptoms and exercise capacity in people with HFpEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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