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ORIGINAL RESEARCH ARTICLE

# Identifying a low-flow phenotype in heart failure with preserved ejection fraction: a secondary analysis of the RELAX trial

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## Abstract

**Aims** The relationship between resting stroke volume (SV) and prognostic markers in heart failure with preserved ejection fraction (HFpEF) is not well established. We evaluated the association of SV index (SVI) at rest with exercise capacity and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in stable patients with HFpEF.

**Methods and results** Participants enrolled in the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial with available data on SVI by the Doppler method were included in this analysis ($n$ = 185). A low-flow state defined by resting SVI $< 35$ mL/m$^2$ was present in 37% of study participants. Multivariable adjusted linear regression analysis suggested that higher resting heart rate, higher body weight, prevalent atrial fibrillation, and smaller left ventricular (LV) end-diastolic dimension were each independently associated with lower SVI. Patients with low-flow HFpEF had lower systolic blood pressure and smaller LV end-diastolic dimension. In multivariable adjusted linear regression models, lower SVI was significantly associated with lower peak oxygen consumption (peak $VO_2$) and higher NT-proBNP levels at baseline, and greater decline in peak $VO_2$ at 6 month follow-up independent of other confounders. Resting LV ejection fraction was not associated with peak $VO_2$ and NT-proBNP levels.

**Conclusions** There is heterogeneity in the resting SVI distribution among patients with stable HFpEF, with more than one-third of patients identified with the low-flow HFpEF phenotype (SVI $< 35$ mL/m$^2$). Lower SVI was independently associated with lower peak $VO_2$, higher NT-proBNP levels, and greater decline in peak $VO_2$. These findings highlight the potential prognostic utility of SVI assessment in the management of patients with HFpEF.

**Keywords** Heart failure with preserved ejection fraction; Stroke volume; Fitness; Biomarkers

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## Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is common, increasing in prevalence, and associated with poor outcomes, similar to HF with reduced EF (HFrEF).[1,2] While significant progress has been made in the management of HFrEF over the past three decades, HFpEF has been challenging to manage with available therapies, and several cardioprotective drugs have failed to modify the natural history of this disease in large randomized control trials.[3] The heterogeneous nature of the pathophysiological abnormalities that underlie HFpEF makes a one-size-fits-all approach challenging.[4] As a result, identifying patients with specific HFpEF phenotypes and modifiable treatment targets may be key for development of novel and effective therapies.

Impairment in aerobic capacity with reduced peak oxygen consumption (peak $VO_2$) is one such modifiable therapeutic target that is associated with worse cardiovascular outcomes.[5] Percent predicted peak $VO_2$ is independently associated with risk of all-cause recurrent admissions.[6] Thus, peak

$VO_2$ and percent predicted peak $VO_2$ are associated with prognosis and may help risk stratify patients with HFpEF. Prior studies have attributed the lower peak $VO_2$ in patients with HFpEF to abnormalities in exercise cardiac output and peripheral oxygen extraction reserve.[7,8] However, the contribution of resting measures of myocardial performance towards exercise intolerance is not well established. Recent studies have identified abnormalities in myocardial contractile parameters in HFpEF such as left ventricular (LV) strain as important prognostic markers.[9,10] Stroke volume (SV), a quantitative measure of myocardial systolic performance, has been associated with long-term clinical prognosis in several diseases such as aortic stenosis, hypertension, HFrEF, and cardiac amyloidosis.[11–15] However, the prevalence of low resting SV and its contribution towards key pathophysiologic abnormalities in patients with chronic stable HFpEF is not well established. Accordingly, we evaluated the prevalence of low resting SV index (SVI) and its association with cross-sectional and longitudinal measures of key prognostic parameters such as exercise capacity and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in a cohort of stable patients with HFpEF. We hypothesize that lower resting SVI in patients with stable HFpEF will be associated with worse exercise capacity and NT-proBNP levels independent of other clinical factors.

# Methods

## Study design and population

The present study was performed as a secondary analysis of the Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial. RELAX was a multi-centre, randomized, double-blind, placebo-controlled trial of patients with HFpEF who were randomized to treatment with sildenafil or placebo.[16] The study design and results of the RELAX trial have been reported previously.[17] In brief, the study included stable patients $>$ 18 years of age with New York Heart Association Class II–IV symptoms, LVEF $\geq$ 50%, low cardiorespiratory fitness [peak $VO_2$ $\leq$ 60% predicted and respiratory exchange ratio (RER) $\geq$ 1.0], and either elevated natriuretic peptide level (NT-proBNP $\geq$ 400 pg/mL or BNP $\geq$ 200 pg/mL) or increased intra-cardiac filling pressures (mean pulmonary capillary wedge pressure $>$ 20 mmHg at rest or $>$ 25 mmHg with exercise). Study participants must have had at least one of the following in the 12 months prior to consent: (i) history of HF hospitalization; (ii) intravenous loop diuretic or haemofiltration for acute HF treatment; (iii) chronic loop diuretic treatment to control HF symptoms with echocardiographic evidence of chronic diastolic dysfunction with left atrial enlargement; or (iv) catheterization for dyspnoea demonstrating increased intra-cardiac filling pressures.

From October 2008 to February 2012, 216 patients were enrolled in the primary trial across centres in the USA and Canada. The primary outcome was change in peak $VO_2$ from baseline to 24 weeks. The National Heart, Lung, and Blood Institute (NHLBI) funded RELAX and the Heart Failure Clinical Research Network (HFCRN) conducted the trial. Each participating site institutional review board approved the trial protocol. All study participants provided written informed consent. The present secondary analysis was prepared using de-identified trial data obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. This study does not necessarily reflect the opinions or views of the RELAX investigators, HFCRN, or NHLBI. The present analysis included all study participants with available data on SVI at baseline.

## Echocardiographic examination

Doppler, M-mode, and two-dimensional echocardiography were performed in all study participants at baseline according to a standard image acquisition and measurement protocol.[17] Triplicate measurements were obtained and reviewed at the echocardiography core laboratory (Mayo Clinic, Rochester, MN). Echocardiographic parameters were assessed using the American Society of Echocardiography and European Association of Echocardiography guidelines.[18] For participants in atrial fibrillation, echocardiographic measurements were averaged over 3–5 beats at the time of examination.[19]

Two-dimensional echocardiography was used to measure LV dimensions. As previously described, the Doppler method for SV assessment was performed.[15,18] SV was estimated using the LV outflow tract (LVOT) velocity-time integral measured by pulsed wave Doppler and the LVOT area. SV was calculated using the following formula: SV = [3.14 × (LVOT diameter/2)$^2$] × LVOT velocity-time integral. For the present analysis, SV was indexed to body surface area.

## Cardiopulmonary exercise testing

RELAX cardiopulmonary exercise testing (CPET) protocols were standardized and have been described previously.[17] In brief, simultaneous CPET and breath-by-breath gas exchange were performed at certified sites. Patients and CPET laboratories selected either cycle or treadmill ergometry as the exercise modality. CPET protocol included ventilatory gas analysis at rest followed by 3 min of low-level exercise with incremental 10 W/min ramp. The treadmill ramp procedure involved a linear increase in speed and curvilinear increase in grade. Standardized encouragement was provided

throughout the protocol to achieve a RER $\geq$ 1.0. To evaluate whether exercise was limited from a pulmonary mechanical limit, Borg dyspnoea scores, forced expiratory volume in 1 s, and forced vital capacity were measured. Quality control measures were used to ensure reliability of results, including CPET core lab evaluation of data (Massachusetts General Hospital, Boston, MA), calibration of equipment, and standardized protocols.

The highest 30 s median $VO_2$ value among measurements within the last 60 s of the symptom-limited CPET protocol was defined as the peak $VO_2$. Modified V-slope method and ventilatory equivalent assessment were used to evaluate anaerobic threshold as previously described.[17] Peak oxygen pulse is the amount of oxygen consumed per heart beat during peak exercise and was calculated from the ratio of peak $VO_2$ and peak heart rate. Peak RER ($VCO_2/VO_2$) indicated patient effort and exhaustion. Chronotropic index was calculated using the following formula: (heart rate at peak exercise − resting heart rate)/[(220 − age) − resting heart rate].[20]

## Serum biomarkers

Haemoglobin and creatinine levels were measured at a local lab; and all other biomarkers of myocardial stress (NT-proBNP), injury [high-sensitivity troponin I (hs-TnI)], fibrosis [pro-collagen III N-terminal peptide (PIIINTP), galectin-3, C-terminal telopeptide of collagen type 1 (CITP)], pulmonary vasoreactivity [endothelin-1 (ET)], and inflammation (high-sensitivity C-reactive protein) were measured at the core laboratory (University of Vermont, Burlington, VT). NT-proBNP was measured using a commercially available assay (Roche Diagnostics, Basel, Switzerland) as previously described.

## Statistical analysis

The primary exposure variable of interest in this analysis was SVI at baseline measured by Doppler echocardiography. SVI was calculated as the product of the LVOT area and LVOT velocity-time integral by pulsed wave Doppler. The main outcome of interest was peak $VO_2$ measured at baseline. Secondary outcomes of interest included baseline measures of NT-proBNP levels and changes in peak $VO_2$ and NT-proBNP levels over 6 month follow-up.

Study participants were stratified according to SVI $<$ or $\geq$ 35 mL/m$^2$, a well-established clinical threshold that is associated with low-flow state or normal-flow state, respectively.[11,21] Baseline demographic, clinical, echocardiographic, and exercise test characteristics were compared with Fisher's exact and Kruskal–Wallis tests for categorical and continuous variables, respectively. Independent clinical predictors of SVI were assessed using a multivariable adjusted regression analysis model that included age, sex, race, resting heart rate, systolic blood pressure, weight, history of diabetes, history of chronic obstructive pulmonary disease (COPD), history of atrial fibrillation, smoking status, haemoglobin, and LV end-diastolic dimension. These covariates were identified *a priori* on the basis of the biological plausibility of their association with SVI and the outcome.

The association of baseline SVI with the primary outcome of interest peak $VO_2$ at baseline was assessed by constructing the following multivariable adjusted linear regression models. Model 1: adjusted for age and sex. Model 2: Model 1 + treatment arm, cardiovascular risk factors and co-morbidities (race, systolic blood pressure, diabetes history, current smoker, creatinine, weight, COPD, atrial fibrillation, haemoglobin). Model 3: Model 2 + NT-proBNP levels. Model 4: Model 3 + additional biomarkers (PIIINTP, hs-TnI, CITP, high-sensitivity C-reactive protein, ET). To better understand the mechanisms through which SVI may modify peak $VO_2$, additional models were also constructed with inclusion of peak oxygen pulse in Model 3. Similar models were also constructed to determine the associations between indexed SV and NT-proBNP levels at baseline. As a sensitivity analysis, we also evaluated the adjusted association of EF, the current standard measure of LV systolic function, with peak $VO_2$ and NT-proBNP levels independent of other potential confounders.

Separate multivariable adjusted models were also constructed to evaluate the associations of baseline SVI with changes in peak $VO_2$ and NT-proBNP levels over 6 month follow-up. These models were adjusted for baseline clinical and demographic characteristics including age, sex, treatment arm, and cardiovascular risk factors and co-morbidities (race, systolic blood pressure, diabetes history, current smoker, creatinine, weight, COPD, atrial fibrillation, haemoglobin), and NT-proBNP (only in model examining change in peak $VO_2$).

# Results

## Baseline characteristics

Among the 216 participants enrolled in the RELAX trial, 185 (86%) had available Doppler SVI and peak $VO_2$ data at baseline and were included in this analysis. *Table S1* compares the baseline characteristics of participants that were included vs. excluded from the present analysis. Compared with the study participants that were included in this analysis, the excluded participants had higher body weight with no other meaningful differences in demographic characteristics or risk factor burden. The distribution of the indexed SV and the key outcomes of interest, peak $VO_2$ and NT-proBNP levels at baseline, are shown in *Figure S1*. Overall, 37.3% of study participants had indexed SV less than the clinical cut-off of


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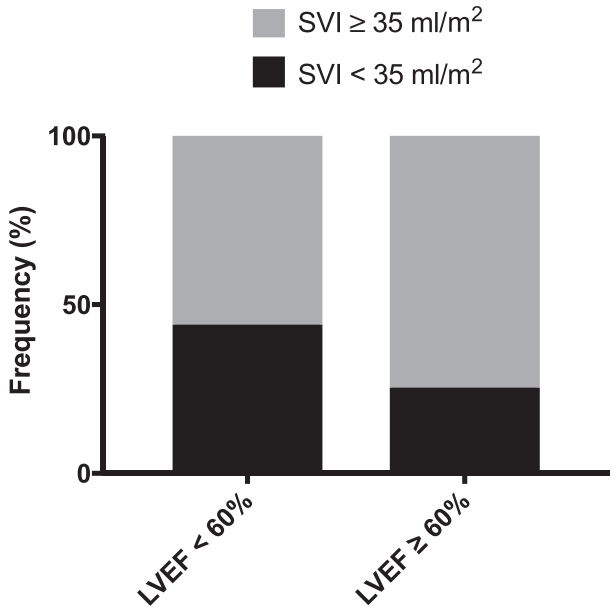
**Figure 1** Frequency of low-flow and normal-flow state indexed by resting stroke volume index and according to left ventricular ejection fraction. LVEF, left ventricular ejection fraction; SVI, stroke volume index.




35 mL/m$^2$ and were identified as having a low-flow phenotype (*Figure 1*). The clinical characteristics of study participants stratified by their baseline SVI (low-flow vs. normal-flow HFpEF phenotypes) are compared in *Table 1*. Study participants with the low-flow phenotype had significantly lower systolic blood pressure, lower rates of current smoking, higher prevalence of atrial fibrillation, lower 6 min walk distance, and higher levels of NT-proBNP and high-sensitivity C-reactive protein. Markers of fibrosis such as PIIINTP were also higher in the low-flow group with a trend towards statistical significance.

Baseline echocardiographic and CPET characteristics are shown in *Table 2*. Patients with low-flow HFpEF had smaller LV end-diastolic dimension and modestly lower EF than patients with normal-flow HFpEF. Among exercise test parameters, peak exercise systolic blood pressure and indexed peak oxygen pulse were significantly lower in the low-flow vs. normal-flow group. Peak $VO_2$ was also lower with a trend towards significance in the low-flow group compared with the normal-flow group in unadjusted comparison.

## Clinical factors associated with stroke volume index

In multivariable adjusted linear regression analysis, higher resting heart rate, higher body weight, presence of atrial fibrillation, and smaller LV end-diastolic dimension were each independently associated with lower SVI (*Table 3*). In contrast, age, sex, race, systolic blood pressure, history of diabetes, history of COPD, smoking status, and haemoglobin were not associated with SVI in the adjusted model.

**Table 1** Baseline demographic, clinical, and laboratory characteristics according to stroke volume index < or ≥ 35 mL/m$^2$

| | SVI < 35 mL/m$^2$ ($n$ = 69) | SVI ≥ 35 mL/m$^2$ ($n$ = 116) | $P$-value |
|---|---|---|---|
| Stroke volume index, mL/m$^2$ | 29.6 (25.3–31.4) | 42.7 (39.3–47.3) | <0.01 |
| Age, years | 69.0 (61.0–78.0) | 69.0 (63.0–77.0) | 0.94 |
| Female, % | 55.1 | 45.7 | 0.23 |
| White, % | 91.3 | 90.5 | 0.18 |
| Weight, lb | 209.0 (192.2–238.1) | 201.7 (173.0–236.5) | 0.22 |
| Systolic blood pressure, mmHg | 120.0 (112.0–130.0) | 132.0 (120.0–144.0) | <0.01 |
| Diastolic blood pressure, mmHg | 71.0 (62.0–78.0) | 70.0 (63.0–77.0) | 0.67 |
| Chronotropic index | 0.47 (0.31–0.63) | 0.49 (0.33–0.63) | 0.97 |
| Current smoker, % | 5.8 | 21.6 | 0.01 |
| Diabetes, % | 40.6 | 42.2 | 0.88 |
| COPD, % | 14.5 | 19.8 | 0.43 |
| Atrial fibrillation, % | 66.7 | 45.7 | 0.01 |
| 6 min walk distance, m | 293.0 (213.0–357.0) | 322.5 (252.0–389.5) | 0.05 |
| Haemoglobin, g/dL | 12.8 (12.3–13.9) | 12.9 (11.8–13.7) | 0.47 |
| Creatinine, mg/dL | 1.2 (0.9–1.5) | 1.2 (0.9–1.5) | 0.81 |
| NT-proBNP, pg/mL | 909.8 (355.6–1971.0) | 603.8 (279.7–1388.0) | 0.02 |
| hs-TnI, pg/mL | 9.8 (4.8–20.9) | 8.7 (5.8–18.5) | 0.99 |
| PIIINTP, μg/L | 8.1 (6.5–10.3) | 7.3 (5.7–9.8) | 0.09 |
| Galectin-3, ng/mL | 13.8 (11.6–18.9) | 13.9 (11.0–18.1) | 0.80 |
| High-sensitivity C-reactive protein, mg/L | 4.9 (2.6–10.5) | 3.2 (1.6–6.6) | 0.01 |
| CITP, μg/L | 5.9 (4.8–9.8) | 6.1 (4.3–9.9) | 0.82 |
| ET, pg/mL | 2.3 (1.9–3.3) | 2.4 (1.9–3.2) | 0.97 |
| Sildenafil treatment, % | 50.7 | 48.3 | 0.76 |
| Beta-blocker, % | 76.8 | 74.1 | 0.73 |

Data presented as median (inter-quartile range) or %. Comparison performed using $\chi^2$ for categorical variables and Kruskal–Wallis for continuous variables.

CITP, C-terminal telopeptide of collagen type 1; COPD, chronic obstructive pulmonary disease; ET, endothelin-1; hs-TnI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIIINTP, pro-collagen III N-terminal peptide; SVI, stroke volume index.

**Table 2** Baseline echocardiographic and cardiopulmonary exercise characteristics according to stroke volume index < or ≥ 35 mL/m$^2$

| | SVI < 35 mL/m$^2$ ($n$ = 69) | SVI ≥ 35 mL/m$^2$ ($n$ = 116) | $P$-value |
|---|---|---|---|
| LVEF, % | 60.0 (55.0–60.0) | 60.0 (60.0–65.0) | <0.01 |
| LV end-diastolic dimension, cm | 4.4 (4.1–5.0) | 4.7 (4.3–5.2) | 0.03 |
| LV end-systolic dimension, cm | 2.8 (2.5–3.2) | 2.9 (2.6–3.3) | 0.49 |
| LA volume, mL | 92.3 (75.5–130.0) | 94.4 (75.3–114.4) | 0.86 |
| Peak anaerobic threshold (mL/kg/min) | 7.3 (6.1–8.4) | 7.7 (6.5–9.0) | 0.13 |
| Peak $VO_2$, mL/kg/min | 11.7 (9.5–13.8) | 12.8 (10.5–14.7) | 0.07 |
| Peak oxygen pulse (mL/kg/beat) | 0.10 (0.09–0.13) | 0.12 (0.10–0.14) | <0.01 |
| Peak RER | 1.1 (1.0–1.2) | 1.1 (1.0–1.2) | 0.02 |
| Peak systolic blood pressure, mmHg | 142.0 (123.0–164.0) | 160.0(138.0–176.0) | <0.01 |
| Peak diastolic blood pressure, mmHg | 71.0 (62.0–80.0) | 70.0 (60.0–80.0) | 0.67 |
| Peak heart rate, b.p.m. | 112.5 (90.5–124.0) | 104.5 (91.5–120.5) | 0.54 |

Data presented as median (inter-quartile range). Comparison performed using $\chi^2$ for categorical variables and Kruskal–Wallis for continuous variables.
LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; RER, respiratory exchange ratio; $VO_2$, oxygen consumption.

## Association of stroke volume index and exercise characteristics

In adjusted linear regression analysis, lower SVI was associated with significantly lower peak $VO_2$ independent of demographic and clinical characteristics (*Table 4*). The significant association between SVI and peak $VO_2$ persisted after further adjustment for NT-proBNP levels and other biomarkers of fibrosis, vasoreactivity, inflammation, and myocardial injury. The association of SVI with peak $VO_2$ was attenuated after additional adjustment for peak oxygen pulse (standard estimate $\beta$ = 0.07, $P$-value = 0.21). The association of SVI with baseline peak $VO_2$ is not modified by age ($P$-value for interaction = 0.4014) or sex ($P$-value for interaction = 0.1561). In contrast with SVI, baseline LVEF was not associated with peak $VO_2$ after adjustment for baseline demographic, clinical characteristics, and NT-proBNP levels (*Table S2*).

Baseline SVI was also significantly associated with longitudinal changes in peak $VO_2$ in adjusted analysis such that lower SVI was associated with greater decline in peak $VO_2$ over 6 month follow-up (*Table 4*). No significant interaction was noted between baseline SVI and sildenafil treatment for changes in peak $VO_2$ on follow-up ($P$-value for interaction = 0.7786).

**Table 3** Baseline factors significantly associated with resting stroke volume

| Predictor of SVI | Standardized $\beta$ | $P$-value |
|---|---|---|
| Resting HR | −0.15 | 0.04 |
| Weight | −0.27 | 0.01 |
| Atrial fibrillation | −0.31 | <0.01 |
| LVEDD | 0.36 | <0.01 |

Standardized $\beta$ represents the change in the outcome (SVI) per standard deviation change in the exposure while keeping other covariates fixed. Variables adjusted for include the following: age, sex, race, resting heart rate, systolic blood pressure, weight, history of diabetes, history of COPD, history of atrial fibrillation, smoking status, haemoglobin, and LVEDD.
HR, heart rate; LVEDD, left ventricular end-diastolic dimension; SVI, stroke volume index.

## Association of stroke volume index and N-terminal pro-B-type natriuretic peptide levels

Because NT-proBNP level distribution was skewed (*Figure S1*), log-transformed NT-proBNP levels were used as the dependent variable in the linear regression models. In multivariable adjusted analysis, SVI was inversely associated with NT-proBNP after adjustment for demographic and clinical characteristics such that lower SVI was associated with higher NT-proBNP levels at baseline (*Table 5*). Additional adjustment for biomarkers of inflammation, vasoreactivity, fibrosis, and myocardial injury did not attenuate the inverse association

**Table 4** Association of baseline stroke volume index with peak oxygen consumption at baseline and on follow-up

| | Standardized $\beta$ per 1 SD higher resting SVI at baseline | $P$-value |
|---|---|---|
| Baseline peak $VO_2$ | | |
| Age, sex adjusted | 0.17 | 0.01 |
| Age, sex, + treatment arm + risk factors adjusted | 0.20 | <0.01 |
| Age, sex, treatment arm, risk factors + NT-proBNP adjusted | 0.15 | 0.03 |
| Age, sex, treatment arm, risk factors, NT-proBNP + other biomarkers adjusted | 0.16 | 0.02 |
| Change in peak $VO_2$ | | |
| Age, sex, treatment arm, risk factors, NT-proBNP adjusted | 0.19 | 0.03 |

Risk factors: race, systolic blood pressure, diabetes history, current smoker, creatinine, weight, COPD, atrial fibrillation, and haemoglobin. Other biomarkers: PIIINTP, hs-TnI, CITP, high-sensitivity C-reactive protein, and ET. Standardized $\beta$ represents the change in the outcome (peak $VO_2$) per 1 SD higher SVI while keeping other covariates fixed.
CITP, C-terminal telopeptide of collagen type I; COPD, chronic obstructive pulmonary disease; ET, endothelin-1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIIINTP, pro-collagen III N-terminal peptide; SD, standardized deviation; SVI, stroke volume index; $VO_2$, oxygen consumption.

**Table 5** Association of baseline stroke volume index with log N-terminal pro-B-type natriuretic peptide at baseline and on follow-up

| | Standardized $\beta$ per 1 SD higher resting SVI at baseline | *P*-value |
|---|---|---|
| Baseline log NT-proBNP | | |
| Age, sex adjusted | −0.20 | <0.01 |
| Age, sex, treatment arm, risk factors adjusted | −0.16 | 0.01 |
| Age, sex, treatment arm, risk factors + other biomarkers adjusted | −0.15 | 0.01 |
| Change in log NT-proBNP | | |
| Age, sex, treatment arm, risk factors adjusted | −0.14 | 0.08 |

Risk factors: race, systolic blood pressure, diabetes history, current smoker, creatinine, weight, COPD, atrial fibrillation, and haemoglobin. Other biomarkers: PIIINTP, hs-TnI, CITP, high-sensitivity C-reactive protein, and ET. Standardized $\beta$ represents the change in the outcome (log NT-proBNP) per 1 SD higher SVI while keeping other covariates fixed.
CITP, C-terminal telopeptide of collagen type I; COPD, chronic obstructive pulmonary disease; ET, endothelin-1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PIIINTP, pro-collagen III N-terminal peptide.

between SVI and NT-proBNP. In contrast, LVEF was not associated with NT-proBNP in adjusted analysis (*Table S2*).

A trend towards statistically significant association between baseline SVI and change in NT-proBNP on follow-up was observed in adjusted analysis (standard estimate $\beta = -0.14$, *P*-value = 0.08). Thus, lower SVI at baseline was associated with a trend towards greater increase in NT-proBNP over 6 month follow-up.

## Discussion

We observed several important findings in our study. First, in a cohort of stable outpatients with HFpEF, there is substantial heterogeneity in the resting SVI distribution despite normal LV systolic function. More than one-third (37%) of study participants had a low-flow phenotype with resting SVI $< 35$ mL/m$^2$. Lower resting SVI was independently associated with significantly lower peak $VO_2$ and higher NT-proBNP levels. Furthermore, in patients with HFpEF, low SVI at baseline was also associated with a greater decline in peak $VO_2$ at 6 month follow-up. Taken together, our study findings highlight the physiological importance of low SVI among patients with HFpEF and identifies a low-flow phenotype that is associated with worse exercise capacity and higher natriuretic peptides—both strong, adverse prognostic markers.

Exercise intolerance is a common clinical manifestation in HFpEF, and prior studies have demonstrated significantly lower peak $VO_2$, an objective measure of exercise capacity, among patients with HFpEF.[22] Low exercise capacity has significant prognostic value in HFpEF, and lower peak $VO_2$ is strongly associated with worse quality of life, higher mortality risk, and higher risk of HF hospitalizations.[5,23] Accordingly, improvement in peak $VO_2$ has been the primary outcome of interest for several randomized controlled trials evaluating therapies for HFpEF.[8,24,25] Findings from our study suggest that low resting SVI may be an important determinant of low baseline peak $VO_2$ and greater longitudinal decline in peak $VO_2$ at short-term follow-up. Similar to peak $VO_2$, we also observed a significant association between low resting SVI and high NT-proBNP levels, another key prognostic marker in HFpEF.[26,27] Future studies are needed to determine if therapeutic strategies targeting improvements in SVI may be effective in improving exercise capacity and clinical outcomes in patients with the low-flow HFpEF phenotype.

The mechanism through which low resting SV may contribute to lower exercise capacity is not well understood. It is noteworthy that the association between resting SVI and peak $VO_2$ was attenuated with adjustment for peak oxygen pulse, the product of peak exercise SV and arterial–venous oxygen content difference. This suggests that the lower levels of peak $VO_2$ in patients with low-flow HFpEF may be related to abnormal exercise SV. We also identified several important clinical features that are associated with the low-flow HFpEF phenotype. In particular, smaller LV end-diastolic volume and higher body weight were independently associated with lower SVI. LV size is an important determinant of SV, and it is plausible that the low-flow phenotype in HFpEF is related to LV–body size mismatch leading to more restrictive physiology and inadequate forward flow at rest as well as during exercise. It is also plausible that the low-flow HFpEF phenotype identifies an early stage of infiltrative cardiac disorders like cardiac amyloidosis, which also manifests with smaller LV end-diastolic volume, restrictive physiology, and impairment in SV.[28] Recent studies have identified wild-type transthyretin amyloidosis in 17–30% of patients with HFpEF.[29–31] Future studies are needed to determine if the low-flow HFpEF phenotype may be related to cardiac deposition of wild-type transthyretin amyloid protein. This is particularly relevant considering the prognostic importance of low SVI in cardiac amyloidosis[14,15] and the recent success of tafamidis, a transthyretin protein stabilizer, in reducing all-cause mortality, cardiovascular hospitalizations risk, and decline in functional capacity in this patient population.[32]

Our study has several important clinical implications for management of patients with HFpEF. The current paradigm of HFpEF diagnosis and management relies on demonstration of normal LVEF in patients with clinical HF. While a normal LVEF is considered a surrogate for normal systolic function, it standardizes SV to LV end-diastolic volume and does not account for low SV in patients with smaller LV end-diastolic volumes. In our study, more than one-third of patients with normal EF demonstrated low SVI. Furthermore, SVI but not LVEF was independently associated with peak $VO_2$ and

NT-proBNP levels. Taken together, these observations demonstrate the importance of assessing and reporting SVI in the management of patients with stable HFpEF. To our knowledge, this is the first study to examine the association of resting SVI with exercise and clinical parameters and identifies a unique phenotype among patients with stable HFpEF. Future studies are needed to determine if patients with a low-flow phenotype of HFpEF have higher risk of clinical adverse events such as HF hospitalization and mortality and may benefit from established as well as novel therapies that are known to improve myocardial performance and SV.

This study has several noteworthy limitations. First, the primary study was restricted to patients who could perform an exercise test, which limits generalizability. Second, we cannot exclude the susceptibility of these results to unmeasured confounding given the study design. Finally, the echocardiographic data were captured at rest, which limits assessment of SV reserve and measures of systolic and diastolic function during exercise.

In conclusion, our study findings suggest that approximately one-third of patients with stable HFpEF have a resting low-flow phenotype despite normal EF. Low resting SVI is independently associated with lower exercise capacity, higher NT-proBNP levels, and greater decline in exercise capacity on longitudinal follow-up. Future studies are needed to determine if the resting low-flow phenotype may identify patients at higher risk of adverse clinical outcomes and may be a target for treatment with well-established as well as novel cardioprotective therapies.

## Conflict of interest

Dr Fonarow reports consulting for Abbott, Amgen, Bayer, Janssen, Novartis, and Medtronic. All other authors report no conflict of interest.

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## Supporting information

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

**Table S1**. Comparison of baseline characteristics of study participants that were included **versus** not included in the study.
**Table S2**. Association of left ventricular ejection fraction with peak oxygen consumption and NT-proBNP levels at baseline
**Figure S1**. Distribution of baseline measures of indexed stroke volume (A), peak oxygen **consumption** (peak **$VO_2$**, B), and **NT-proBNP** levels (C).

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