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Influence of Left Ventricular Stroke Volume on Incident Heart Failure in a Population with Preserved Ejection Fraction (From the Strong Heart Study)

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Abstract

At a given level of left ventricular (LV) systolic function, LV pump performance (assessed by stroke index [SVi]) may differ, depending on LV size. We evaluated whether low SVi may be considered a marker of risk for incident congestive heart failure (HF), independent of LV geometry and systolic function, assessed by ejection fraction (EF) or midwall fractional shortening (MFS), in a large population-based sample with normal EF. Clinical and echocardiographic data from the second Strong Heart Study (SHS) exam, including 2,885 American Indians (59±8 years; 63% women) with normal EF (EF≥51% in men and EF≥55% in women) and without prevalent HF or significant valve disease, were analyzed. Low SVi was defined as SVi≤22 ml/$m^{2.04}$. Low SVi was more common among men and associated with lower body mass index, systolic blood pressure, LV mass index, left atrial dimension, EF and MFS, and with higher relative wall thickness. During a mean 12-year follow-up, 209 participants developed HF and 246 had acute myocardial infarction. In Cox-regression analysis, low SVi was associated with higher risk of incident HF

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Conflicts of interest:
None.

(HR=1.38; 95% C.I.=1.06–1.80), independently of age, sex, body mass index, heart rate, hypertension, prevalent cardiovascular disease, left atrial dimension index, LV mass index, LV concentric geometry, EF or MFS and abnormal wall motion, also accounting for myocardial infarction as a competing risk event. In conclusion, in the SHS, low SVi was associated with higher incident rate of HF, independently of LV geometry and systolic function and other major confounders.

Keywords

LV pump performance; LV systolic function; stroke volume; heart failure

Left ventricular (LV) systolic function, assessed most commonly by ejection fraction (EF), strongly predicts cardiovascular outcome[1,2]. However, if the mitral valve is continent, a given level of EF does not invariably correspond to a given stroke volume (SV), an indicator of LV pump performance[3], because SV depend on LV end-diastolic volume and recruitment of Starling forces. Accordingly, beyond the level of EF, incidence of heart failure (HF), might be also related to reduced SV. Both parameters of LV systolic function (EF) and pump performance (SV) are influenced by LV geometry[4–6]. LV dilatation favours greater SV[3], which might have beneficial effects on symptoms and outcome, despite it increases LV wall stress and LV mass, both negative prognosticators[4]. In contrast, a low SV is often associated with small LV chamber volume in the presence of concentric LV geometry, which has negative impact on cardiovascular phenotype and outcome[4–6]. At the present, whether low SV is associated with higher risk of incident HF, independently of LV geometry and function, in a general population with normal EF, has not yet been evaluated. Accordingly, the present study was undertaken to explore whether low SV predicts incident HF, independently of LV geometry and function and other major confounders, in the large population-based cohort of participants in the Strong Heart Study (SHS).

METHODS

We analyzed the SHS, a population-based cohort study of cardiovascular risk factors and disease in American Indians. A detailed description of the study design and methods has been previously reported[7–10]. At the enrolment, a total of 4,549 American Indian men and women, aged 45 to 74 years, from 3 communities in Arizona, 7 in south-western Oklahoma and 3 in South and North Dakota, participated in the first SHS examination, conducted from 1989 to 1991 (phase 1). The cohort was followed and re-examined every four years. The phase 2 examination evaluated 89% of all of the surviving members of the original cohort, who also underwent standard Doppler echocardiogram. Thus, the second SHS examination was used as baseline for the present analysis.

For the present study, we included 2,885 SHS participants with preserved EF and without prevalent HF or echocardiographic evidence of valve dysfunction, defined by any valve stenosis or more than mild mitral or aortic regurgitation, and with available follow-up data. Institutional Review Boards of the participating institutions and the participating tribes approved the study and submission of the paper.

The SHS used a standard methodology at each clinical examinations[10], including a personal interview, physical examination with anthropometric and blood pressure measurements, and morning blood sample collection after a 12-h fasting, performed at local community settings and Indian Health Service clinics by the study staff.

Arterial hypertension was defined as blood pressure≥140/90 mmHg or current antihypertensive treatment. Obesity was classified as body mass index≥30 kg/m^2. Waist circumference was used as indicators of central adiposity. Diabetes was defined as fasting glucose≥126 mg/dl or use of antidiabetic treatment. Albuminuria was defined as urinary albumin/creatinine ratio≥30 mg/g, measured on a single spot urine sample[7–10]. Glomerular filtration rate was estimated by the simplified Modification of Diet in Renal Disease formula.

Echocardiograms were performed using phased-array machines, with M-mode, two-dimensional and Doppler capabilities, as previously reported[11,12]. Echocardiograms were evaluated in the Core Laboratory at the Weill-Cornell Medical College by expert readers blinded to the participant's clinical details, using a computerized review station (Digisonics, Inc., Houston, TX) equipped with digitizing tablet and monitor screen overlay for calibration and performance of each needed measurement. Reproducibility of echocardiographic measures has been tested in the Weill Cornell adult echo-lab in an ad-hoc designed study[13].

The LV internal dimensions and wall thickness were measured at end-diastole and endsystole as previously reported[11,12]. LV mass was calculated using an autopsy-validated formula and normalized by height to the allometric power of 2.7[14]. Relative wall thickness was measured as the sum of LV posterior and septal wall thickness/LV internal diameter ratio at end-diastole and normalized for age[15]. LV concentric geometry was considered present if age-normalized relative wall thickness exceeded 0.41[15]. Left atrial dimension was measured in parasternal long axis view using the trailing edge-to-leading edge method. Due to geometric consistency (all linear measures), left atrial dimension and LV end-diastolic diameter were ratiometrically normalized for height in meters.

SV was calculated as the difference between LV end-diastolic and end-systolic volumes by the z-derived method[16]. Similar to what has been done with LV mass, SV and cardiac output were normalized by height in meters to the respective allometric powers of 2.04 (Stroke index [SVi]) and 1.83 (Cardiac index [COi]), extracted from a reference normal weight, normotensive adult population sample[17]. Low SVi was defined according to the cut-off derived in aortic stenosis studies[18], as SVi≤ 22/m$^{2.04}$, which corresponds to the previously reported cut-off of 35 ml/m^2 when normalized for body surface area[19].

EF was obtained by the ratio of SV to end-diastolic volume. Preserved EF was defined using gender specific partition values previously obtained in a reference population from the SHS[20]: EF<51% in men and EF<55% in women, respectively. Because abnormal LV geometry can influence LV systolic function measured at the chamber level[4,21], midwall fractional shortening (MFS), a geometry-independent parameter of LV systolic function, was also computed using a previously reported formula[21]. LV wall motion was assessed by a visual, semi-quantitative method in parasternal long- and short-axis, and apical views[22] and

considered normal when all segments had wall thickening ≥30% or abnormal in presence of segmental or hypokinesis, akinesis or diskinesis[22].

Cardiovascular events were recorded and adjudicated as previously reported[7–10]. The endpoint of the present analysis was the first occurrence of congestive HF, defined by Framingham criteria for congestive HF. HF was diagnosed when two major, or one major and two minor Framingham criteria were present concurrently in the absence of a condition such as end-stage renal failure leading to massive fluid overload. Major criteria were: paroxysmal nocturnal dyspnoea or orthopnoea, neck vein distention, rales, cardiomegaly, acute pulmonary oedema, S3 gallop, venous pressure>16 cm water or hepato-jugular reflux. Minor criteria were: ankle oedema, night cough, dyspnoea on exertion, hepatomegaly, pleural effusion, vital capacity<2/3 of predicted or heart rate≥120 beats/minute. Weight loss≥4.5 kg in 5 days in response to treatment could serve as either major or minor criterion.

Statistical analysis was performed using IBM-SPSS 21.0 software (IBM Corporation, Armonk, NY) and expressed as mean ± standard deviation for continuous and as proportions for categorical variables. Variables not normally distributed are reported as median and interquartile range, and log transformed. Indicator variables for field center were entered as covariates in all multivariate analyses. Participants were categorized in 2 groups according to the presence of normal or low SVi. Descriptive statistics included analysis of variance and χ^2 test. Analyses of covariance or binary logistic regression analyses were run to adjust for age, sex, systolic blood pressure and body mass index (for variables not already normalized for body size). Multivariable Cox proportional hazard was performed to test the association of low SVi with incident HF, using a backward building procedure, adjusting for age, sex, body mass index, hypertension, heart rate, prevalent cardiovascular disease, LV mass index, LA dimension index, concentric LV geometry, EF (or MFS) and presence of abnormal LV wall motion. Due to possible cause-effect relationship with incident HF, acute myocardial infarction, occurring before the first diagnosis of HF, was also censored as a “competing risk event”[23]. Attention was paid to avoid substantial multi-collinearity by checking linear variance inflation factor in the final models. The 2-sided significance level used was 0.05.

RESULTS

Among the 2,885 SHS participants (59±8 years; 63% women) with normal EF and without prevalent HF included in this analysis, prevalence of arterial hypertension, obesity and diabetes was 44%, 54%, and 47%, respectively. Prevalent cardiovascular disease was present in 213 participants (7%). Low SVi was found in 536 (19%) of the study population. Table 1 shows that participants with low SVi, were more likely to be men, with lower prevalence of obesity and hypertension, but higher heart rate.

Table 2 shows that left atrial dimension, LV end-diastolic diameter, LV mass index, EF and MFS were lower in participants with low than in those with normal SVi. Consistently, participants with low SVi exhibited low prevalence of LV hypertrophy, but their relative wall thickness and the prevalence of concentric geometry were higher than in individuals with normal SVi. The between-group differences in the echocardiographic parameters were also

confirmed after adjusting for potential confounders including age, sex, body mass index, and systolic blood pressure.

During a mean of 12-year follow-up (12 ±4 years), 246 incident acute myocardial infarctions and 209 HF events occurred.

Participants with initial low SVi exhibited greater incidence of myocardial infarction than those with normal SVi (12% versus 8%, p=0.003), but, apparently, no significant difference in incident HF (8% versus 7%, p=0.7). This could be largely attributable to the association of low LV mass index with low SVi.

In multivariable Cox regression, indeed, low SVi was associated with more than 80% increased chance of incident HF (HR=1.84; 95% C.I.=1.19–2.84, p=0.005), independently of significant effect of older age, male sex, prevalent hypertension and/or CV disease, higher heart rate, and greater left atrial dimension and LV mass index. Concentric geometry, EF (or, alternatively, MFS), and presence of abnormal wall motion did not enter this final predictive model. Table 3 shows that the effect of low SVi was confirmed also when the intervening myocardial infarction before the censoring of HF was analyzed as a competing risk event.

DISCUSSION

The present study provides the first population-based evidence that reduced LV pump performance, assessed by low SVi, is a strong predictor of incident HF, independently of significant confounders, including LV geometry and function and left atrial dimension, in individuals with initial normal EF. The implication of our findings is that LV systolic function (assessed by EF) and pump performance (assessed by SVi) are not concordant in the prediction of incident HF. This disagreement is likely to explain the evidence of the poor prognosis and higher risk of HF in patients with concentric LV geometry in the setting of preserved EF[24]. EF can remain normal during chronic pressure overload by use of the preload reserve[25] or by changes in LV geometry[4]. Similar to the phenotype described in low-flow aortic stenosis[19], our results demonstrate that, also in a general context, low SVi is typically associated with smaller cardiac chamber dimensions and concentric LV geometry. Concentric LV geometry is reported to enhance EF, due to the effect of cross-fiber shortening and thickening amplifying the rate of cardiomyocyte contraction at the endocardial level[4,6]. Thus, we also considered in our analyses the MFS, an index of LV systolic function that is independent of LV geometry[4,26]. Interestingly, we found that low SVi predicts incident HF, independently of LV concentric geometry, MFS and also abnormal wall motion. Thus, our results suggest that, independently of LV systolic function, low SVi is an important risk for incident HF and might have an important role in the clinical manifestations of HF. We can speculate that in the contest of preserved EF, HF might result from low SVi related to increased wall thickness, associated reduction of LV chamber dimensions, and increased left atrial dimension, a potent marker of diastolic dysfunction[27]. These characteristics are easily detectable by 2-D echocardiography in every context, even in the absence of Doppler interrogation[28].

Also intriguing is the observation that low SVi is associated in univariate analyses with cardiovascular characteristics (lower LV mass and left atrial dimension) that would be protective in relation to the risk of HF or any other incident major cardiovascular event. In contrast, in a multivariable Cox model, low SVi became potently associated with incident HF, as a high-risk characteristic in addition to increasing left atrial dimension. These characteristics, low SVi and dilated left atrium, might be common in both HF with reduced and preserved EF, as suggested by the evidence provided by the persistence of the 2 variables in the model also when acute myocardial infarction (the leading cause of systolic HF) was considered as a competing risk event. Although our design is purely observational and no cause-effect relationship may be inferred, this observation can be used as a hypothesis to test in ad hoc designed studies.

Our results adds to a previously report in a population of treated hypertensive patients with electrocardiographic evidence of LV hypertrophy[5]. Both studies provided evidence that the negative outcome associated with low SVi was independent of LV mass and geometry. Higher LV mass is a powerful marker of adverse outcome, but is also positively related to chamber volume, and therefore, especially in the presence of normal EF, to higher SV[29], which might have protective effect. In our analysis, high LV mass index remained an independent predictor of HF together with low SVi and great left atrial dimension, but the effect was lost when myocardial infarction was analyzed as a competing risk event. We may assume that this difference is related to the fact that, in the competing-risk event model, most of the prediction is related to myocardial infarction-independent HF, thus most likely HF with preserved EF, a type of HF not necessarily related to amount of LV mass, but rather to diastolic dysfunction, associated with left atrial dilatation, and concentric LV geometry, of which low SVi is the functional consequence. In contrast, LV mass joins low SVi and large left atrial dimension in the generic prediction of HF. We do not have the possibility to discriminate the two types of HF, but our findings can be used for more advanced research on this issue.

Unfortunately our study did not include advanced echocardiographic techniques such as tissue Doppler or strain imaging, since these were not available at the time of the 2nd SHS exam. However, simple LV linear dimensions can be easily obtained in usual clinical settings and in a number of consolidated cohorts and registries to calculate parameters of LV systolic function and pump performance, favoring the applicability and reproducibility of our methods in other epidemiological studies, as well as in clinical practice.

Given the ethnic peculiarity of the SHS, our findings might not necessarily be generalizable and might need to be verified in other populations with different genetic and environmental backgrounds, especially because algorithms for risk prediction might be substantially affected by prevalence and distribution of individual risk factors[30]. Further research is needed to determine the applicability of the present findings in other populations with different ethnic composition and lower prevalence of obesity.

In conclusion, this study shows that LV performance assessed by SVi is an independent marker of risk of incident HF in a general North American Indian population with initially

normal EF. Further studies are needed to elucidate the progression to clinically overt HF, and clarify the role of the co-factors in precipitating the type of HF.

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Table 1

Baseline clinical characteristics in participant with normal or low left ventricular stroke index

Variable	Stroke index		p
	Normal (N=2,349)	Low (N=536)	
Age (years)	59 ± 8	59 ± 7	0.08
Men	748 (32%)	321 (60%)	0.0001
Body surface area (m^2)	1.90 ± 0.20	1.92 ± 0.22	0.03
Body mass index (kg/m^2)	32 ± 6	28 ± 5	0.0001
Waist girth (cm)	108 ± 14	102 ± 14	0.0001
Obesity	1379 (59%)	180 (34%)	0.0001
Systolic blood pressure (mmHg)	130 ± 20	126 ± 19	0.0001
Diastolic blood pressure (mmHg)	75 ± 10	77 ± 10	0.001
Heart rate (bpm)	67 ± 10	71 ± 11	0.0001
Hypertension	1070 (46%)	209 (39%)	0.006
Glomerular filtration rate ($ml/min/1.73m^2$)	79 (68–94)	80 (68–94)	0.71
Albuminuria	775 (33%)	182 (34%)	0.76
Low density lipoprotein cholesterol (mg/dl)	119 ± 33	120 ± 34	0.33
High density lipoprotein cholesterol (mg/dl)	42 ± 13	41 ± 15	0.26
Triglycerides (mg/dl)	130 (92–184)	135 (92–198)	0.14
Smoker	719 (31%)	186 (35%)	0.08
Diabetes mellitus	1098 (47%)	257 (48%)	0.63
Prevalent cardiovascular disease	167 (7%)	46 (9%)	0.24
Prevalent coronary artery disease	136 (6%)	40 (7%)	0.16

Obesity defined as body mass index≥30 kg/m^2

Hypertension defined as blood pressure≥140/90 mmHg or current antihypertensive treatment

Table 2

Baseline cardiac characteristics in participant with normal or low LV stroke index.

	Stroke index			
Variable	**Normal (N=2,349)**	**Low (N=536)**	**p**	**Adjusted p**
Left atrial dimension (cm)	3.6 ± 0.4	3.3 ± 0.5	0.0001	0.0001
Left atrial dimension index (cm/m)	2.2 ± 0.3	2.0 ± 0.3	0.0001	0.0001
LV end-diastolic diameter (cm)	5.0 ± 0.4	4.6 ± 0.4	0.0001	0.0001
LV end-diastolic diameter index (cm/m)	3.1 ± 0.2	2.7 ± 0.1	0.0001	0.0001
LV end-systolic diameter (cm)	3.2 ± 0.4	3.0 ± 0.4	0.0001	0.0001
Septal thickness (cm)	0.9 ± 0.1	0.9 ± 0.1	0.78	0.05
Posterior wall thickness (cm)	0.9 ± 0.1	0.8 ± 0.1	0.06	0.50
LV mass (g)	157 ± 34	134 ± 31	0.0001	0.0001
LV mass index ($g/m^{2.7}$)	42 ± 9	32 ± 7	0.0001	0.0001
LV hypertrophy	513 (22%)	12 (2%)	0.0001	0.0001
Relative wall thickness	0.36 ± 0.05	0.39 ± 0.06	0.0001	0.0001
Concentric LV geometry	117 (5%)	93 (17%)	0.0001	0.0001
Stroke volume (ml)	74 ± 11	59 ± 7	------	------
Stroke index ($ml/m^{2.04}$)	27 ± 4	20 ± 2	------	------
Cardiac output (l/min)	4.9 ± 1.0	4.1 ± 0.8	0.0001	0.0001
Cardiac index ($l/min \times m^{-1.83}$)	2.0 ± 0.4	1.6 ± 0.3	0.0001	0.0001
Ejection fraction(%)	66 ± 5	63 ± 5	0.0001	0.0001
Midwall fractional shortening (%)	18 ± 2	16 ± 2	0.0001	0.0001
Abnormal wall motion	79 (3%)	48 (9%)	0.0001	0.02

Adjusted p: for the impact of age, sex, study center, BMI and systolic BP

Table 3

Impact of low left ventricular stroke index on incident heart failure, accounting for incident myocardial infarction as competing risk event.

	HR	95 % C.I.	p
Age (× 5 years)	1.10	1.05–1.20	0.002
Heart rate (× 5 bpm)	1.10	1.05–1.15	0.0001
Hypertension	1.45	1.17–1.80	0.001
Prevalent cardiovascular disease	1.91	1.41–2.56	0.0001
Left atrial dimension index (cm/m)	2.58	1.73–3.83	0.0001
Abnormal wall motion	1.61	1.07–2.40	0.02
Low stroke index	**1.38**	**1.06–1.80**	**0.02**

Sex, body mass index, left ventricular mass index, concentric geometry, ejection fraction (or midwall fractional shortening) did not enter in the final model.