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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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) examination, 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 (hazard ratio 1.38; 95% confidence interval 1.06 to 1.80), independently of age, gender, 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. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;119:1047−1052)

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 dilation favors 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 enrollment, a total of 4,549 American Indian men and women, aged 45 to 74 years, from 3 communities in Arizona, 7 in southwestern 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

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re-examined every 4 years. The phase 2 examination evaluated 89% of all 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 article.

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-hour fasting, performed at local community settings and Indian Health Service clinics by the study staff.

Arterial hypertension was defined as blood pressure $\geq 140/90$ mm Hg 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, 2-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, Texas) 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 echocardiography laboratory in an ad hoc designed study.[13]

The LV internal dimensions and wall thickness were measured at end-diastole and end-systole 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. Because of the 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 cutoff derived in aortic stenosis studies,[18] as SVi $\leq 22/m^{2.04}$, which corresponds to the previously reported cutoff 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 $\geq 51\%$ in men and EF $\geq 55\%$ 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 $\geq 30\%$ or abnormal in presence of segmental hypokinesis, akinesis, or dyskinesis.[22]

Cardiovascular events were recorded and adjudicated as previously reported.[7−10] The end point of the present analysis was the first occurrence of congestive HF, defined by Framingham criteria for congestive HF. HF was diagnosed when 2 major or 1 major and 2 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 dyspnea or orthopnea, neck vein distention, rales, cardiomegaly, acute pulmonary edema, S3 gallop, venous pressure >16 cm water or hepatojugular reflux. Minor criteria were ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, and vital capacity <2/3 of predicted or heart rate ≥ 120 beats/min. 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, New York) and expressed as mean $\pm$ SD 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 chi-square test. Analyses of covariance or binary logistic regression analyses were run to adjust for age, gender, 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, gender, 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. Because of possible cause-effect relation 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 multicollinearity by checking linear variance inflation factor in the final models. The 2-sided significance level used was 0.05.