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ORIGINAL ARTICLE

Assessment of Prevalence, Clinical Characteristics, and Risk Factors Associated With "Low Flow State" Using Cardiac Magnetic Resonance

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Abstract

Objective: To assess prevalence, clinical characteristics, and risk factors associated with low flow state (LFS) in a multiethnic population with normal left ventricular ejection fraction (LVEF).

Patients and Methods: The study included 4398 asymptomatic participants undergoing cardiac magnetic resonance from July 17, 2000, to August 29, 2002. Left ventricular (LV) mass, volume, and myocardial contraction fraction were assessed. Low flow state was defined as stroke volume index (SVi of <35 mL/m^2). Clinical characteristics, cardiac risk factors, and cardiac magnetic resonance findings were compared between LFS and normal flow state (NFS) groups (NFS: SVi of ≥35 mL/m^2).

Results: There were significant differences in the prevalence of LFS in different ethnic groups. Individuals with LFS were older (66±9.6 vs 61±10 years; $P<.0001$). The prevalence of LFS was 19% in the group aged older than 70 years. The logistic multivariable regression analysis found that age was independently associated with LFS. The LFS group had significantly higher prevalence of diabetes (30% vs 24%; $P=.001$), LV mass-volume ratio (1.13±0.22 vs 0.91±0.15; $P<.0001$), inflammatory markers, a lower LV mass index (59±10 vs 65±11 kg/m2; $P<.001$), lower myocardial contraction fraction (58.1±10.6% vs 75.7±13%; $P<.001$), and a lower left atrial size index (32.2±4.6 vs 36.7±5.9 mm/m2; $P<.0001$) than NFS.

Conclusion: Low flow state may be considered an under-recognized clinical entity associated with increasing age, multiple risk factors, increased inflammatory markers, a lower LV mass index, and suboptimal myocardial performance despite the presence of normal LVEF and absence of valvular disease.

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Left ventricular (LV) stroke volume (SV) has been used to evaluate native valvular disease and prosthetic valve function. When the SV index (SVi) calculated by echocardiography is <35 mL/m2, it is defined as a low flow state (LFS).[1] Previous studies reported that LFS was present in ~30% of severe aortic stenosis (AS) and was associated with unfavorable outcomes.[2-8] However, there is little data on LFS in the general population. Furthermore, when LFS is present in individuals with normal LV ejection fraction (LVEF of ≥55%), the condition is often named paradoxical LFS.[9-12] Our recent study found that paradoxical LFS was present in 42% of asymptomatic Hispanic population with normal LVEF and no AS.[13] This unexpectedly high prevalence of LFS in the Hispanic population needs further verification using advanced imaging modalities, such as cardiac magnetic resonance (CMR), to eliminate the potential underestimation of SV by echocardiography.[14] In addition, prevalence of LFS in other ethnic populations is unknown. If LFS is indeed common in an asymptomatic population with normal LVEF, what are its clinical characteristics? Are there any demographic characteristics, cardiac risk factors, or

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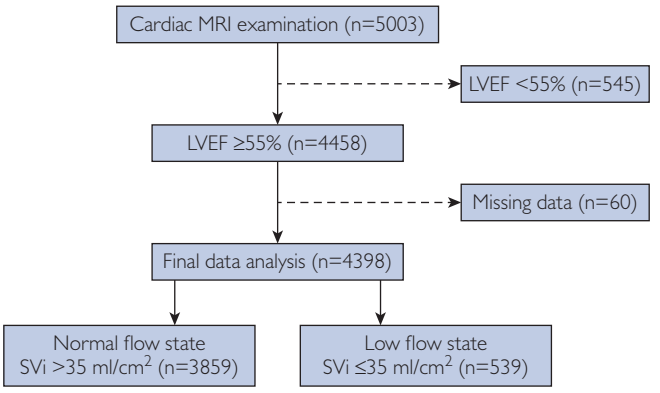

FIGURE 1. Illustration of study participants and CMR data analysis work-flow of multiethnic study of atherosclerosis. CMR, cardiac magnetic resonance.

myocardial performance associated with it? All these important questions remain to be answered.

The multiethnic study of atherosclerosis (MESA) was a population-based sample of 6814 men and women who were 45-84 years old without clinical evidence of cardiovascular (CV) disease. Approximately 38% of the cohort was White, 28% Black, 23% Hispanic, and 11% Asian. The primary objective of the study was to determine the clinical characteristics related to the progression of subclinical CV disease.[15] This study analyzed 5003 CMR studies and correlated CMR findings with prevalence, clinical characteristics, and risk factors associated with LFS using the baseline database collected in MESA. The findings from this CMR study would provide new insight into LFS and stimulate further investigation of its clinical significance.

METHODS

Study Population

The study included 6814 asymptomatic participants in the MESA study, which prospectively collected clinical characteristics and CV risk factors from participants who were free of overt CV disease at enrollment. Cardiac magnetic resonance was performed on 5003 participants at baseline. In the data analysis, 545 participants were excluded owing to a LVEF of <55% and an additional 60 participants were excluded owing to missing partial data (Figure 1). Consequently, a total of 4398 participants were included in the final data analysis. Standardized questionnaires were used to obtain medical histories of hypertension, diabetes, and cardiac risk factors. Baseline laboratory studies were collected. The study was approved by the Institutional Research Board, and informed consents were obtained from all participants.

CMR Study

Cardiac magnetic resonance was performed as part of the baseline examination using 1.5-T magnets for the measurement of LV dimension, mass, function, and volumes using a fast gradient echo cine sequence, as previously reported.[16] Twelve short axis slices, one 4-chamber view, and one 2-chamber view were acquired. Low-flow state was defined as SVi of <35 mL/m^2 and the normal flow state (NFS) as SVi of ≥35 mL/m^2. Left ventricular myocardial contraction fraction (MCF) was calculated by dividing SV by myocardial volume, which was defined as LV myocardial mass divided by the mean density of myocardium (1.05 g/mL). The mean wall thickness was the average of the mid inferior septum, superior septum, anterior wall, superior lateral, interior lateral wall, and interior wall in mid slices. The left atrial (LA) sizes were measured

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TABLE 1. Comparisons of Demographic and Clinical Characteristics Between Normal Flow and LFS[a]

Variables	NFS SVi ≥35 mL/m^2 (n=3859)	LFS SVi <35 mL/m^2 (n=539)	*P*
Age (y), mean ± SD	60.91±10	65.5±9.6	<.001
Woman (%)	2089 (54.1%)	310 (57.5%)	.14
Weight (kg)	76.8±16.2	76.4±15.8	.57
Height (m)	1.7±0.1	1.67±0.1	.21
BMI (kg/m^2)	27.7±5.0	27.8±4.9	.87
BSA (cm^2)	1.84±0.2	1.84±0.2	.4
Waist circumference (cm)	96.2±13.1	98.2±12.8	.001
Hip circumference (cm)	104.4±10.4	104.9±10.6	.31
Waist-to-hip ratio	0.92±0.08	0.94±0.07	<.001
Hypertension (%)	1627 (42.2)	230 (42.7)	.82
Diabetes (%)	902 (23.4)	160 (29.7)	.001
SBP (mmHg)	125.2±21.5	125.8±19.4	.53
DBP (mmHg)	71.6±10.1	71.0±10.6	.23
Heart rate (bpm)	61.9±9.1	66.9±10.0	<.001
Laboratory test results			
Fasting glucose (mg/dL)	95.2±26.9	100.9±38.9	.001
Total cholesterol (mg/dL)	194.1±35.0	196.5±37.8	.17
LDL-C (mg/dL)	116.9±30.8	118.5±33.6	.31
HDL-C (mg/dL)	51.6±15.1	50.1±14.0	.02
Triglycerides (log)[b]	4.7±0.5	4.8±0.5	.0001
eGFR (mL/min/1.73m^2)	78.5±15.8	74.9±15.5	<.001
IL-6 (log)[b]	0.14±0.7	0.28±0.6	<.001
CRP (log)[b]	0.56±1.2	0.74±1.1	.0005
Medications			
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (%)	578 (14.98)	98 (18.18)	.05
β-Blocker (%)	346 (8.98)	40 (7.43)	.24
CCB (yes %)	478 (12.39)	51 (9.46)	.05
Diuretics (%)	456 (11.83)	78 (14.5)	.08

[a]BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein-cholesterol; IL, interleukin; LFS, low flow state; LDL-C, low density lipoprotein-cholesterol; SBP, systolic blood pressure.

[b]Triglycerides, IL6, and CRP distributions were right-skewed. Normal distributions were obtained by log transformation. Hypertension was defined as blood pressures of ≥140/90 mmHg (Eighth Joint National Committee Hypertension Guideline). Diabetes was defined as any participant who self-reported a physician diagnosis, used diabetic medication, a fasting glucose 126 mg/dL, or a nonfasting glucose of 200 mg/dL.

in 456 patients in an additional ancillary study.[17] Cardiac magnetic resonance was initially performed using a traditional fast gradient echo cine sequence. However, steady-state free precession cine (SSFP) is currently the standard of care for CMR. Therefore, the baseline CMR database obtained using a traditional fast gradient echo cine sequence was systematically converted to the SSFP CMR database, which was used in this study.[18]

Statistical Analyses

The *t* test or χ^2 tests were used for continuous or categorical variable comparisons, respectively. As interleukin (IL)-6 and C-reactive protein (CRP) distributions were right-skewed, normal distribution was obtained by log transformation. Logistic regression was conducted for multivariable analysis of risk factors associated with LFS-using variable selections on the basis of backward elimination

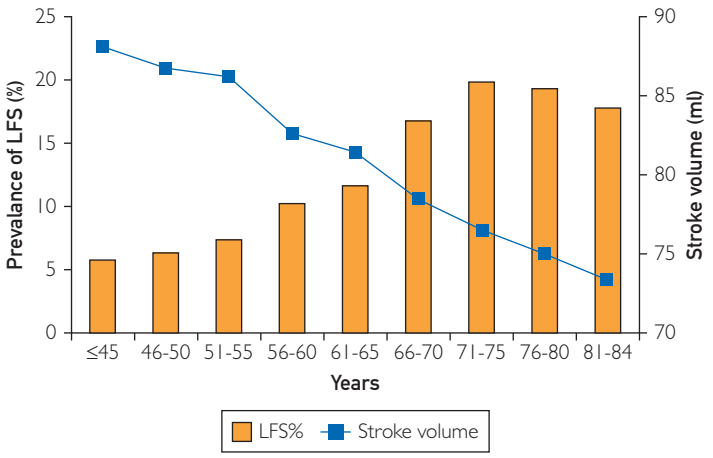

FIGURE 2. Prevalence of LFS and changes in SV in different age groups are illustrated. The SV gradually decreased and the LFS increased with increasing age. LFS, low flow state; SV, stroke volume.

and clinical relevance. All statistical analyses were performed using SAS 9.4.

RESULTS

Comparisons of Demographic and Clinical Characteristics Between NFS and LFS

There were no differences in weight, height, and body mass index (BMI, calculated as the weight in kilograms divided by the height in meters squared) between LFS and NFS (Table 1). However, the LFS group had significantly higher waist circumference, higher waist-to-hip ratio, higher fasting glucose levels, higher triglyceride levels, higher prevalence of diabetes (30% vs 24%; P=.001), higher IL (IL-6: 0.14±0.66 vs 0.28±0.62; P<.001) and CRP (0.56±1.17 vs 0.74±1.07; P=.005).

Prevalence of LFS in Different Ethnic Groups

The average prevalence of LFS in the whole MESA study group was 12%. The prevalence significantly increased with age, whereas SV gradually decreased with age (Figure 2). There were also significant differences in the prevalence of LFS among the ethnic groups (African American 16%, White 13%, Chinese 10%, and Hispanic 9%; P<.001). Table 2 compares demographic characteristics among 4 different

TABLE 2. Comparison of Ages, Heights, Weights, BSA, Waist-to-Hip Ratio and Stroke Volume Among Different Ethnic Groups[a]

	White (n=1705)	African American (n=1087)	Hispanic (n=983)	Chinese (n=623)	*P*
Ages (y), mean ± SD	62.0±10.1	61.5±9.9	60.4±10	61.6±10.4	<.01
Height (cm)	168.7±9.7	168.3±9.7	161.8±9.1	161.6±8.7	<.01
Weights (kg)	78.1±16.0	83.7±15.9	75.8±13.5	62.5±11.0	<.01
BSA (cm^2)	1.88±0.22	1.93±0.21	1.80±0.18	1.66±0.17	<.01
Waist-to-hip ratio	0.92±0.08	0.91±0.07	0.95±0.07	0.91±0.07	<.01
Stroke volume (mL)	83±19	84±19	82±18	73±15	<.01
SVi (mL/m^2)	44.1±8.4	43.3±8.3	45.4±8.3	44.2±7.2	<.01

[a]BSA, body surface area; SVi, stroke volume index. Values are expressed in mean ± SD.

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TABLE 3. Comparisons of CMR Measurements Between NFS and LFS[a]

Variables	NFS SVI >35 mL/m^2 (n=3859)	LFS SVI ≤35 mL/m^2 (n=539)	*P*
Stroke volume index (mL/m^2)	46.01±6.97	31.19±3.4	<.001
LV stroke volume (mL)	85.03±17.33	57.22±9.01	<.001
Cardiac output (L/min)	5.98±1.41	4.46±0.96	<.001
Cardiac output index (L/min/m^2)	3.24±0.68	2.44±0.47	<.001
LVEDV (mL)	132.51±26.83	94.78±15.35	<.001
LVESV (mL)	47.49±12.3	37.56±7.66	<.001
LV ejection fraction (%)	64.31±4.55	60.49±3.53	<.001
Mean LV end-diastolic wall thickness (mm)	9.09±1.71	9.82±2.03	<.001
LV mass (g)	120.43±28.18	106.6±24.55	<.001
LVMI indexed by BSA (g/m^2)	65.33±11.1	58.95±9.72	<.001
LVM percentage predicted (%)	87.23±13.12	78.12±11.65	<.001
Mass-to-volume ratio	0.91±0.15	1.13±0.22	<.001
LA diameter index (mm/m^2)	36.7±5.9	32.2±4.6	<.001
Myocardial contraction fraction (%)	75.7±13%	58.1±10.6%	<.001

[a]CMR, cardiac magnetic resonance; NFS, normal flow state; LA, left atrial; LFS, low flow state; LV, left ventricle; LVM, left ventricular mass; LVEDV, left ventricular end-diastole volume; LVESV, left ventricular end-systole volume; LVMI, left ventricular mass index; SVi, stroke volume index. Values are expressed in mean ± SD.

ethnic groups. Whites had the oldest age, African Americans had the largest body surface area (BSA), Hispanics had the highest waist-to-hip ratio, and Chinese had the lowest SV. In comparison with the White participants, African Americans had an increased odds ratio (OR) to have LFS (OR, 1.269; 95% CI, 1.013-1.588; $P<.05$). The Chinese (OR, 0.73; 95% CI, 0.537-0.991; $P<.05$) and Hispanic (OR, 0.603; 95% CI, 0.458-0.794; $P<.001$) participants had lower OR for LFS relative to the White ethnic group with age, sex, race, heart rate, and triglyceride in the model.

Features of LV Remodeling and Function

There were significant differences in CMR parameters between the LFS and NFS groups. The SV, SVi, cardiac output (CO), CO index, LVEF, MCF, LV volumes, LV mass, and LV mass index were significantly lower in LFS than NFS groups (all $P < .001$) (Table 3). Although LV mass-to-volume ratios were higher in LFS, the LV mass index and LA size indexes were significantly lower in the LFS than NFS groups, suggesting that patients with LFS underwent LV concentric remodeling without hypertrophy, as reflected by decreases in LV mass and mass index) or LV dimensions.

DISCUSSION

This is the first study to assess LFS in a large multiethnic population using CMR. Several interesting findings were observed: (1) LFS was relatively common in elders with preserved LVEF despite the absence of valvular disease, in particular AS; (2) LV mass index, LVEF, MCF, and LA size were significantly lower in the LFS group in comparison with the NFS group; and (3) LFS was associated with advanced age, cardiac risk factors, adverse LV remodeling, and suboptimal myocardial performance (Table 1).

Factors Associated With LFS

Previous MESA investigators observed that traditional CV risk factors were associated with LV size, mass, and volume, in particular that low density lipoprotein, impaired fasting glucose, and diabetes were associated with a decrease in LV SV.[19] This study found that age exhibits a particularly strong association with reduced SVi (Figure 2). The findings were consistent with clinical observation of a high incidence of LFS in senile patients with

AS who underwent transcatheter aortic valve replacement.[20] Previous studies found that age is associated with a particular phenotype of LV remodeling marked by an increased mass-to-volume ratio. This pattern of remodeling confers significant CV risk, particularly when it is present earlier in life.[21] This study found that LFS was present in 19% of participants older than 70 years. A substantial reduction in SV was the main contributor to LFS in the senile population (Figure 2). The features of LV remodeling and function in LFS were characterized by an increase in mass-to-volume ratio with a decrease in LV mass index (concentric remodeling without hypertrophy), lower CO index, lower LVEF, and suboptimal myocardial performance. Previous studies found that physical activity increases LV mass, SV, and decreases mass-volume ratio[22,23] without significant concentric remodeling,[24,25] suggesting that the phenotype of concentric remodeling with reduced LV mass and SV in the setting of LFS may be potentially associated with a decrease in physical activity in some senile populations.

Previous studies suggested that multiple biological pathways may lead to LV concentric remodeling. Several investigators found that many CV risk factors were associated with LV concentric remodeling (hypertension, a high BMI, an increase in body fat, insulin resistance, and diabetes).[26-28] This study found that there are significantly more CV risk factors in the LFS group than the NFS group (Table 1), and similar findings were reported in patients with AS and LFS.[10] The LFS group had significantly higher IL-6 and CRP levels than the NFS group. Caminit et al[29] reported that inflammation may be driven by abnormal adiposity (an increasing waist-to-hip ratio), which may be linked to LV remodeling process.[30]

Diastolic dysfunction may cause an elevated LV end-diastolic pressure, which limits LV filling, leading to an increase in LA pressure, dilated LA with long-term exposure, and a decrease in SV. In this study, we used indexed LA size as a surrogate marker for the long-term effects of diastolic dysfunction and LA pressure elevation. Our study found that indexed LA size was significantly lower in the LFS than the NFS groups, suggesting that diastolic dysfunction is unlikely to be the primary cause of low SV in these asymptomatic populations. The MCF is a volumetric measure of myocardial shortening independent of LV size and geometry and is an important predictor of mortality in patients with or without valvular disease.[31,32] This study reported that LVEF, SV, CO, CO index, and MCF were significantly lower in the LFS group than in the NFS group, which suggests that the LFS group may have suboptimal myocardial performance than the NFS group (Table 3).

This study also found that there are significant differences in the prevalence of LFS among different ethnic groups. African Americans experience the highest prevalence of LFS, and Hispanics had the lowest prevalence of LFS. The higher weight and larger BSA in African Americans may account for a higher prevalence of LFS than in other ethnic groups. For this reason, heights, weights, BMI, BSA, obesity, and their measurements should be considered when identifying LFS. Previously, investigators reported that the LV mass-to-volume ratio was associated with a higher BMI, an increased waist-to-hip ratio, and a larger waist circumference.[33] In this study, nonindexed CO, nonindexed SV, and nonindexed LV mass were also significantly lower in the LFS than the NFS groups, which indicated that an increase in BSA was not a primary cause of LFS in the general population. Whether differences in genetics,[34] cardiac risk factors, lifestyle, inflammation, physical activity, or other factors directly or indirectly contribute to the development of LFS merits continued investigation. Furthermore, additional studies may determine if modification of lifestyles (weight loss, increasing physical activities, or diabetes prevention) would reduce the risk of developing LFS.

Clinical Implication

Approximately 30% of patients present with low-flow, low-gradient, severe AS, particularly in those with advanced age who underwent transcatheter aortic valve replacement.[20] Valve area calculations and pressure gradients are highly flow-dependent. Pre-existing LFS often generates a small aortic valve area and a low gradient, potentially leading to the overdiagnosis of low-flow, low-gradient, severe AS or prosthesis-patient mismatch.[35,36] This study found that most LFS may be considered an

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intrinsic or pre-existing condition with or without AS in many patients rather than a paradoxical phenomenon or primary consequence of AS. This is evidenced by high incidence of LFS (>40%) even after elimination of AS by transcatheter aortic valve replacement procedure.[37,38] An increase in SV by exercise could eliminate 70% of low-gradient severe AS as aortic valve area (AVA) increased to >1.0 cm.[2,39] A high prevalence of LFS in the senile population suggests that criteria for severe AS may be different in the elderly compared with the younger population (younger than 70 years). The current guideline proposed the same criterion for the diagnosis of severe AS and the selection of intervention regardless of age, race, and clinical characteristics. This approach appeared not to produce satisfactory outcomes in some low-flow AS.[40] Healthy aging or physical activity may have a pleotropic effect on CV and metabolic health. Further studies are warranted to identify the key determinants of the severity of AS (velocity, pressure gradient, valve area, or additional parameters) and to determine appropriate indications for intervention in the presence of LFS.

Previous studies found that LV mass, volume, and systolic function might have some association with traditional CV risk factors.[19] This study found that LFS was associated with increased inflammatory markers and metabolic changes (increased glucose, increased triglyceride, decreased high density lipoprotein, increased waist circumferences, and increased waist-to-hip ratio); all suggest proneness to metabolic syndrome or predispose to clinical heart failure with preserved ejection). Clinicians would speculate that LFS might carry prognostic implications. Previous studies have reported that low flow or low SVi was independently associated with unfavorable outcomes in AS, which could be potentially considered as indirect evidence of the adverse effect of LFS on outcomes. Further studies of the prognostic significance of LFS in general population are warranted.

Study Limitations

The concept of LFS has not been investigated using CMR in a large cohort of asymptomatic individuals with normal LVEF and no valvular disease. Therefore, it is still unknown if the definition and cutoff values for LFS (SVi of <35 mL/m^2) initially proposed on the basis of echocardiographic studies will be the same as by CMR because SV may be underestimated by 2-dimensional echocardiography in comparison with CMR.[41,42] It still remains unknown if LFS represents particular LV remodeling in response to aging or reflects adverse LV remodeling resulting from cardiac risk factors, genetic factors, inflammation, or other environmental factors (diets, or physical activities). Cardiac magnetic resonance is not an ideal tool to assess diastolic dysfunction in a large population owing to high costs and the lack of standard diagnostic criteria.

Although LA enlargement is often associated with elevated atrial pressure caused by diastolic dysfunction, LA volume or volume index may reflect changes in LV geometry in 3-dimensions more accurately than linear measurement. However, the baseline MESA study did not have LA volume data. Therefore, LV size index was used in this study. Low LVEF and MCF in LFS group may suggest occult systolic dysfunction. Global longitudinal strain was not measured in the baseline CMR study. However, our previous study reported that the patients with LFS had lower global longitudinal strain than the NFS group.[13] Increase in afterloads may influence LVEF and SV. However, there was no significant difference in systolic pressures between the LFS and NFS groups, suggesting afterload might not be a primary factor causing lower LVEF or SV in the LFS groups.

CONCLUSION

This study revealed that LFS is common in a senile population with normal LVEF in the absence of valvular disease. It is associated with reduced SV, unfavorable clinical characteristics, multiple risk factors, and suboptimal myocardial performance.

POTENTIAL COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations and Acronyms: **AS,** aortic stenosis; **BSA,** body surface area; **BMI,** body mass index; **CMR,** cardiac magnetic resonance; **DBP,** diastolic blood pressure; **DM,** diabetes mellitus; **LFS,** Low flow state; **LV,** left ventricular; **LVEF,** left ventricular ejection fraction; **LVEDV,** left ventricular end-diastole volume; **LVESV,** left ventricular end-systole volume; **MCF,** myocardial contraction fraction; **MESA,** multiethnic study of atherosclerosis; **SBP,** systolic blood pressure; **SV,** stroke volume; **SVi,** stroke volume index

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