Echocardiographic Investigation of Low-Flow State in a Hispanic/Latino Population

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Abstract

Objective: To assess the prevalence of low-flow state (LFS) with left ventricular (LV) stroke volume index of less than 35 mL/m² and the demographics, clinical and echocardiographic characteristics associated with LV remodeling and function in a Hispanic/Latino population.

Participants and Methods: The study included 1346 asymptomatic participants from the Hispanic Community Health Study/Study of Latinos with normal LV ejection fraction (≥55%) and no valvular heart disease. LV volume, mass and left atrial volume, LV ejection fraction, global longitudinal strain, and myocardial contraction fraction were measured by echocardiography. The participants were divided into LFS or normal flow state (NFS: stroke volume index ≥35 mL/m²). Demographics, clinical and echocardiographic characteristics, and measures of LV remodeling and function were compared between the LFS and NFS groups.

Results: The prevalence of LFS was 41%. In comparison with NFS, the LFS had lower LV mass index (77.2±0.96 g/m² vs 84.6±0.86 g/m²; P<.001), left atrial volume index (20.6±0.39 mL/m² vs 23.5±0.37 mL/m²; P<.001), global longitudinal strain (−16.8±0.16% vs −17.7±0.17%; P<.001), and myocardial contraction fraction (43.3±0.63% vs 55.7±0.64%; P<.001). There was no significant difference in the relative wall thickness (LFS: 0.40±0.004 vs NFS: 0.40±0.005; P=.57). The LFS group had significantly higher hemoglobin A1c (6.18±0.07% vs 5.97±0.04%; P=.01) than the NFS group.

Conclusion: A high prevalence of LFS associated with echocardiographic characteristics reflecting unfavorable LV remodeling and function was observed in a Hispanic/Latino population. Further studies of the prognostic significance of LFS in a large multiethnic population are warranted.

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Currently, the prevalence of LFS in the Hispanic/Latino population is unknown. We hypothesized that LFS could be preexistent before the development of clinically apparent heart disease and might be associated with decreased myocardial performance or LV functional impairment in comparison with NFS. This study aims to assess the prevalence of LFS and its association with demographics, clinical and echocardiographic characteristics, and cardiac function in a Hispanic/Latino population. The population-based Hispanic Community Health Study/Study of Latinos is a prospective study with an echocardiographic substudy well suited to the study purpose. To our knowledge, this is the first investigation of LFS in a large Hispanic/Latino population-based sample.

PARTICIPANTS AND METHODS

Study Population
The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a multicenter population-based cohort study of 16,415 Hispanic/Latino adults recruited from 4 United States communities (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California) from 2008 to 2011. The population was recruited from persons reporting the following origins: Mexican, Puerto Rican, Dominican, Cuban, Central American, and South American. Baseline examinations included a wide array of medical, social, demographic, and economic measurements, as described previously. The Echocardiographic Study of Latinos (ECHO-SOL) is an ancillary study, which recruited 1824 participants from the HCHS/SOL for the assessment of cardiac structure and function. HCHS/SOL participants were eligible for inclusion in ECHO-SOL if they were within 36 months of their initial HCHS/SOL visit. Of the 1824 participants recruited for ECHO-SOL, 478 participants were excluded because of LVEF <55% or valvular heart disease (defined as more than mild valvular stenosis or regurgitation), after which 1346 met the inclusion criteria for final data analysis. There were 501 men and 845 women with a mean age of 55±0.45 years. The study was approved by the institutional review boards of the sponsoring institutions and participants consented to study inclusion.

Echocardiography Study
Standard Doppler transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography. Echocardiographic images were acquired at each field imaging center, including 2-dimensional (2D), M-mode, spectral, color, and tissue Doppler. Digital images were transferred to the central core laboratory and interpreted by an experienced echocardiographer before the data were sent to the HCHS/SOL coordinating center. LV remodeling and volumes were assessed using 2D echocardiographic parameters, including LV end-diastolic and endsystolic volumes (by modified Simpson method). LV mass was calculated using the method of Devereux. Apical 2D images in DICOM format were used for the calculation of LV global longitudinal strain (GLS) based on 2D speckle-tracking technology. Myocardial contraction fraction (MCF) was defined as the ratio of SV to myocardial volume, and myocardial volume was calculated as the LV mass divided by the specific gravity of the myocardium (1.05 g/cm³). LV diastolic function was graded according to the American Society of Echocardiography guidelines. All echocardiographic measurements and interpretations were made blinded to clinical and laboratory tests. LFS was defined as SVi <35 mL/m² calculated by Doppler echocardiography using the continuity equation from the LV outflow tract (LVOT).

Clinical Variables
Demographic and clinical variables included age, sex, height, weight, body mass index (BMI; calculated as the body weight in kilograms divided by the height in meters squared), body surface area (BSA; calculated using the DuBois formula), waist and hip circumference in centimeters, hemoglobin A1c and diabetes diagnosis, systolic blood pressure and antihypertensive use, serum lipid levels, and heart rate. The data were collected and managed according to the previously published HCHS/SOL protocol.

Statistical Methods
Statistics consisted of mean and standard error for continuous variables and percentages for categorical variables. If the distribution of the continuous variable was not normal, median
quartiles 1 and 3 were used to describe it. Participants were divided into the NFS (SVi ≥35 mL/m²) and LFS (SVi <35 mL/m²) groups. Clinical, demographic, and echocardiographic characteristics were compared between these 2 groups. The student’s t test was used for normally distributed continuous variables and the chi-square test was used for categorical variables. Echocardiographic measurements were adjusted for sex using linear regression models. Survey procedures in SAS 9.4 (SAS Institute) software were used to account for the sampling weights, stratification, and clustering in HCHS/SOL with inference to the target population. A P value of <.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics
The comparisons of demographic and clinical characteristics between the LFS and NFS groups are presented in Table 1. The prevalence of LFS was 41%. The proportion of women was slightly higher in the LFS group compared with the NFS group (67.5% vs 59.6%; P=.003). There were no significant differences in age, BMI, BSA, waist circumference, or waist-to-hip ratio between the LFS and NFS groups. Compared with those with NFS, participants with LFS tended to be slightly shorter in stature (161.7±0.43 vs 163.4±0.45 cm; P=.004). LFS was associated with a higher hemoglobin A1c (6.18±0.07% vs 5.97±0.04%; P=.01) but no significant difference in the prevalence of clinical diabetes (29.7% vs 28.1%; P=.75). Systolic BP was lower (134.0±0.99 vs 137.7±0.96 mm Hg; P=.01) and heart rate was mildly higher (69±0.6 vs 64±0.4 bpm; P<.001) in the LFS group than in the NFS groups. There was no statistically significant difference in the proportion of the participants taking antihypertensive medications between the LFS and NFS groups (24.9% vs 29.9%; P=.12). The prevalence of LFS in each age group was similar (Figure 1). Although BMI tended to gradually decrease with age, there were no significant differences between the LFS and NFS groups (Figure 2).

Comparisons of Echocardiographic Measurements
Echocardiographic measurements are presented in Table 2. Compared with those with

| TABLE 1. Comparisons of Demographic and Clinical Characteristics Between the LFS and NFS Groupsa,b |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Parameter       | LFS (n=547)     | NFS (n=799)     | P value         |
| Age (y)         | 54.7±0.44       | 55.7±0.46       | .06             |
| Female (%)      | 67.5            | 59.6            | .003            |
| BMI (kg/m²)     | 30.3±0.32       | 30.0±0.23       | .52             |
| BSA (m²)        | 1.85±0.01       | 1.86±0.01       | .41             |
| Weight (kg)     | 79.2±0.89       | 80.3±0.78       | .32             |
| Height (cm)     | 161.7±0.43      | 163.4±0.45      | .004            |
| Waist (cm)      | 100.1±0.80      | 100.5±0.61      | .66             |
| Waist-to-hip ratio | 0.93±0.005     | 0.94±0.004      | .10             |
| Systolic BP (mm Hg) | 134.0±0.99   | 137.7±0.96      | .01             |
| Proportion taking antihypertensives (%) | 24.9          | 29.9            | .12             |
| Heart rate (beats/min) | 69±0.59      | 64±0.42         | <.001           |
| Triglycerides (mg/dL) | 148.6±4.22    | 144.8±4.01      | .53             |
| Total cholesterol (mg/dL) | 208.9±2.09   | 210.6±2.36      | .60             |
| LDL cholesterol (mg/dL) | 128.6±1.70   | 132.3±2.07      | .18             |
| Hemoglobin A1c (%) | 6.18±0.07     | 5.97±0.04       | .01             |
| Proportion with diabetes (%) | 29.7          | 28.1            | .75             |

aBMI, body mass index; BP, blood pressure; BSA, body surface area; LDL, low-density lipoprotein; LFS, low-flow state; NFS, normal flow state.

bData presented as mean with standard error unless otherwise noted.
NFS, the LFS group had lower LVEF (58.8±0.30% vs 60.4±0.28%; \(P<.01\)), smaller LV end-diastolic volume (71.7±1.0 vs 82.3±1.3 mL; \(P<.001\)), lower 2D SV (44.8±0.57 mL vs 52.2±0.71 mL; \(P<.001\)), lower Doppler SV (55.4±0.46 mL vs 80.0±0.72 mL; \(P<.001\)), smaller LVOT diameter (1.84±0.01 cm vs 2.03±0.01 cm; \(P<.001\)), lower LVOT velocity—time integral (VTI) (21.1±0.16 cm vs 24.9±0.18 cm; \(P<.001\)), and lower LV mass index (LVMI) than the NFS group (77.2±0.96 g/m\(^2\) vs 84.6±0.86 g/m\(^2\); \(P<.001\)). LFS was associated with significantly lower GLS (−16.8±0.16% vs −17.7±0.17%; \(P<.001\)) and lower MCF (43.3±0.63% vs 55.7±0.64%; \(P<.001\)) in comparison with NFS. Using a cutoff of −15% to define abnormal GLS, 23% of participants with LFS had abnormal GLS compared with 14% of those with NFS (\(P<.001\)). About

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**FIGURE 1.** The prevalence of low-flow state (LFS) in different age groups.

**FIGURE 2.** Comparison of body mass index (BMI) between low-flow state and normal flow state in different age groups. SVi, stroke volume index.
32.7% of the participants with LFS had Grade II-III diastolic dysfunction compared with 39.9% of those with NFS (P = .05). However, the left atrial (LA) diameter (3.19 ± 0.03 cm vs 3.35 ± 0.02 cm) and LA volume index were significantly lower in the LFS group compared with the NFS group (20.6 ± 0.35 mL/m² vs 23.5 ± 0.37 mL/m²). LVMI was consistently lower in the LFS group than the NFS group across all age groups (Figure 3). There were no statistical differences in relative wall thickness across different age groups (Figure 4).

**DISCUSSION**

To our knowledge, this is the first population-based study to examine the prevalence, demographics, clinical and echocardiographic characteristics of LFS in Hispanics/Latinos. There were several interesting findings: (1) LV volumes, LA volume index, and LVMI were significantly lower in LFS; (2) there was no significant LV concentric remodeling and/or hypertrophy with LFS; (3) LVEF, GLS, and MCF were significantly lower in the LFS group than the NFS group; and (4) hemoglobin A1c was statistically higher in the LFS group than the NFS group. Although the terminology of LFS has been referenced in many publications addressing AS there is little data on LFS in a Hispanic/Latino population without valvular disease. This study provides a perspective on LV remodeling; systolic and diastolic function; and the demographic, clinical, and echocardiographic characteristics associated with LFS in a Hispanic/Latino population. Traditionally, the cause of LFS was often thought to be due to LV hypertrophy (LVH; increased LVMI) and LV concentric remodeling (increased relative wall thickness), which is often associated with hypertension or AS. The current study revealed that LFS is associated with a different type of LV remodeling, which was characterized by a decrease in LV mass (no LVH).

**TABLE 2. Comparisons of Echocardiographic Measurements Between the LFS and NFS Groups<sup>a,b</sup>**

| Parameter                      | LFS (n=547)  | NFS (n=799)  | P value |
|--------------------------------|--------------|--------------|---------|
| LVEF (%)                       | 58.8±0.30    | 60.4±0.28    | <.001   |
| LVEDV (mL)                     | 71.7±1.0     | 82.3±1.31    | <.001   |
| LVESV (mL)                     | 29.2±0.52    | 32.4±0.59    | <.001   |
| 2D SV (mL)                     | 44.8±0.57    | 52.2±0.71    | <.001   |
| IVSd (cm)                      | 1.05±0.01    | 1.09±0.01    | <.001   |
| PWTV (cm)                      | 0.87±0.01    | 0.90±0.01    | .05     |
| LVIDd (cm)                     | 4.40±0.02    | 4.59±0.03    | <.001   |
| Relative wall thickness        | 0.40±0.004   | 0.40±0.005   | .57     |
| LA diameter (cm)               | 3.19±0.03    | 3.35±0.02    | <.001   |
| LA volume index (mL/m²)        | 20.6±0.35    | 23.5±0.37    | <.001   |
| LVOT diameter (cm)             | 1.84±0.01    | 2.03±0.01    | <.001   |
| LVOT VTI (cm)                  | 21.1±0.16    | 24.9±0.18    | <.001   |
| Doppler SV (mL)                | 55.4±0.46    | 80.0±0.72    | <.001   |
| Cardiac output (mL/min)        | 3755±43      | 5077±54      | <.0001  |
| LV mass (g)                    | 144.2±2.22   | 158.7±2.05   | <.001   |
| LV mass index (g/m²)           | 77.2±0.96    | 84.6±0.86    | <.001   |
| LV mass/LVEDV ratio            | 1.95±0.03    | 1.88±0.02    | .056    |
| GLS (%)                        | -16.8±0.16   | -17.7±0.17   | <.001   |
| Grade II-III diastolic dysfunction (%) | 32.7 | 39.9 | .05 |
| Myocardial contraction fraction (%) | 43.3±0.63 | 55.7±0.64 | <.0001 |

<sup>a</sup>GLS, global longitudinal strain; IVSd, interventricular septum thickness; LA, left atrium; LFS, low-flow state; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; 2D SV, 2-dimensional stroke volume; LVIDd, left ventricular internal diameter during diastole; LVOT, left ventricular outflow tract; NFS, normal flow state; PWTV, posterior wall thickness; SV, stroke volume; VTI, velocity–time integral.

<sup>b</sup>Data presented as mean with standard error unless otherwise noted.
lower LA volume index, lower cardiac performance, and a relatively higher LV mass to LV end-diastolic volume (LVEDV) ratio (concentric remodeling, \(P = .056\)). LFS had a relatively high prevalence in our Hispanic/Latino population (41%), which has not been previously recognized.

Prior studies have shown that 13% of patients with hypertension could have LV concentric remodeling without hypertrophy.\(^2,3\)

In the current study, the study population with LFS had lower systolic blood pressure than those with NFS, suggesting that hypertension (increased afterload) is less likely the primary pathophysiology of LFS. In addition, there was no statistically significant difference in the use of antihypertensive medications between LFS and NFS suggesting that antihypertensive therapy did not appear to lead to LFS by either natriuretic effect on LV volume or...
decreased heart rate. There were no consistent patterns of concentric LV remodeling in either LFS or NFS with both groups having a mean relative wall thickness of less than 0.42 (Figure 4). A previous study reported that diabetes might play some role in LV concentric remodeling. The current study found that hemoglobin A1c levels were statistically higher in the LFS group than in the NFS group. This suggests that there might be a greater proportion of undiagnosed diabetes or worse glycemic control in the LFS group. It may be interesting to conduct longitudinal studies to determine if the incidence of clinical diabetes increases in the LFS group or if better glycemic control would decrease or retard the development of LFS.

Diastolic dysfunction may cause elevated LV end-diastolic pressure, which could potentially limit left ventricular filling and lead to an increase in LA pressure, LA dilation, and a reduction in SV. In this study, we specifically assessed diastolic function using Doppler echocardiography and LA volume index (an indirect surrogate for the long-term effect of diastolic dysfunction and increase in LA pressure). The study found that the LA volume index was significantly lower in the LFS than NFS groups, suggesting that diastolic dysfunction is unlikely the primary cause of LFS. In addition, the high prevalence of LFS in the asymptomatic participants suggested that LFS is unlikely caused by a restrictive cardiomyopathy. Long-term follow-up of diastolic function in the LFS population may give a definitive answer to the relationship between LFS and diastolic dysfunction.

Our study found that LVEF and GLS were significantly lower in the LFS group. Measurement of LVEF and GLS can be impacted by LV chamber size. When LV end-diastolic volume is small, LV wall motion during systole may be relatively limited. Reduced GLS in smaller LV cavity sizes has been reported in prior LV geometric modeling experiments. Therefore, whether lower LVEF and GLS in the LFS group is a primary cause for LFS warrants further investigation. The current study found that LFS had significantly lower MCF than NFS. The Multi-Ethnic Study of Atherosclerosis (MESA) reported that low MCF was associated with increased risk for cardiovascular events (myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death) in participants with preserved LVEF. Framingham Heart Study reported that participants in the lowest-quartile MCF were 7 times more likely to develop cardiovascular death, myocardial infarction, stroke, or new heart failure (hazard ratio, 7.11; \( P = .01 \)) in comparison with the remaining quartiles.

Age has been considered a possible contributing factor to low LV volume and concentric remodeling. In prior studies, decreased LV volumes were observed in elderly participants, although LV volume indices were not significantly reduced in older participants. The MESA study had reported that age is associated with a particular phenotype of LV remodeling marked by a decrease in SV, increased mass-to-volume ratio, and increased LVEF. The current study found a nonsignificant trend toward higher LV mass-to-volume ratio, but significantly lower LVEF and MCF in the LFS group, which suggests that age might be related to, but not the only factor contributing to LFS. Further, our study did not observe a significant difference in the ages of the LFS and NFS groups and our study population did not have many elderly participants (mean age, 55 years). An ongoing cardiac MRI study in the MESA population (mean age, 62 years old) may clarify the effect of age on LFS.

The current study used Doppler echocardiography to calculate SV based on the continuity equation. Our previous study reported that the accuracy of SV may be impacted by the appropriate measurement of the diameter of the LVOT. However, the current study found that LVOT VTI was significantly lower in the LFS group than in the NFS group suggesting that the discrepancy in LVOT diameter measurement was less likely the mechanism for LFS. LV volumes measured by 2D echocardiography were also significantly smaller in the LFS group than in the NFS supporting that the low-flow calculated by Doppler echocardiography was indeed low. Cardiac outputs were significantly lower in LFS than in NFS, suggesting that the slightly higher heart rates observed in this study were less likely the primary source for SVi. Calculation of LV mass by 2D echocardiography requires measurements of LV wall thickness and dimensions of LV chambers.
The basal or upper septal hypertrophy may lead to overcalculation of LV mass and particular attention has been paid to the appropriate measurement of wall thickness in the study protocol. In this study, both the thickness of the septum and LVEDV were lower in the LFS group than in the NFS group, which could contribute to lower LV mass in the LFS group.

SV is calculated by indexing SV (numerator) by BSA (denominator). Mathematically, an increase in BSA without a concomitant increase in SV leads to reduced SVi. However, in our study population, there were no significant differences in weight, BMI, and waist-to-hip ratios between those with LFS and NFS. Both SVs calculated by Doppler and 2D echocardiography were significantly lower in the LFS group than in NFS, indicating that LFS is primarily associated with SV rather than increased BSA. About 7.7% of those with LFS and 2.6% of those with NFS (P<.001) had their LVEDV values below the normal reference values reported by the American Society of Echocardiography (LVEDV: 62-150 mL in male participants; 46-106 mL in female participants).18 A recent study reported that lower normal limits for SVi calculated by Doppler echocardiography for ages of 41-65 years were 24.6 mL/m² for men and 24.2 mL/m² for women, which are significantly lower than the cutoff value for LFS (SVi <35 mL/m²).32 Therefore, most participants in our study had their LVEDV, LVMI, and SVi within the reference values.31

Clinical Implication
The current study found that LFS is highly prevalent (41%) in an asymptomatic Hispanic/Latino population with normal LVEF and without concentric LVH. Therefore, LFS may not be considered a “paradoxical” phenomenon. However, LFS may become clinically apparent when an individual develops concentric LVH associated with AS. Our study population with LFS had lower SV, LVEF, and GLS suggesting that LV volume and/or functional reserve in LFS is less robust than in NFS. In addition, MCF is a novel quantitative measure of an index of myocardial performance (output of blood volume per unit of the myocardium) and can be significantly abnormal in the presence of normal LVEF,33 and low MCF is also associated with an unfavorable prognosis.26,27 Our LFS group had significantly lower MCF than the NFS group. The studies from Mayo Clinic reported that aortic intervention for low-flow low-gradient “severe AS” might not produce optimal results10,34 reminding us that afterload (AS) reduction alone may not lead to a satisfactory clinical outcome in the LFS population.4,6 Clinical management of low-flow, low-gradient AS needs to consider multiple factors (reducing afterload, improving myocardial performance, SV, etc).32 Further investigations of the clinical significance of LFS in a multi-ethnic population without AS are warranted.

Study Limitations
There are several limitations in the current study. First, this study was based on the baseline clinical and echocardiography data from ECHO-SOL and we do not have longitudinal outcomes data, although a long-term follow-up is planned. The high prevalence of LFS may be partially a sequela of limitations of Doppler echocardiography. However, all of our studies were read by expert echocardiographers at a single core laboratory, which should reduce variations. Although the Doppler SVi estimation is dependent on the measurement of the LVOT,37 those with LFS had lower LVOT VTI, smaller LV volumes, small LA volume index, and lower 2D SV suggesting that LFS is not solely attributable to the measurement of the LVOT diameter. Our target population had very few individuals over the age of 70, which may limit generalizability to the geriatric population. The prevalence of LFS may vary with the methods used for calculation of SV as a recent study reported that there were significant differences in SV calculated by 2D, 3D, or Doppler echocardiography.31

CONCLUSION
A high prevalence of LFS with unique LV remodeling (concentric remodeling without LVH) and preserved LV function has been under-recognized in the Hispanic/Latino population. This phenotype of LFS presents with lower LV volumes, LA volume index, LV mass, LVMI, LVEF, myocardial strain, and myocardial performance. Further studies of the prognostic significance of LFS in a multi-ethnic population are warranted.
POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

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Abbreviations and Acronyms: AS, aortic stenosis; BMI, body mass index; BSA, body surface area; ECHO-SOL, Echocardiographic Study of Latinos; GLS, global longitudinal strain; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; LA, left atrium; LFS, low-flow state; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass index; LVOT, left ventricular outflow tract; MCF, myocardial contract fraction; NFS, normal flow state; SVI, stroke volume index; VTI, velocity–time integral

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