Research Letter

Characterization of Sympathetic Innervation in Heart Failure With Preserved Ejection Fraction

Heart failure (HF) with reduced ejection fraction (HFrEF; LVEF <40%) is a disorder in which there is renin-angiotensin (RAS) and sympathetic nervous (SNS) system activation as a consequence of primary myocardial dysfunction. In contrast, in HF patients with LVEF >50% (ie, HF with preserved ejection fraction [HFpEF]), evidence for such neurohormonal activation is sparse,[1] and studies examining neurohormonal antagonists in HFpEF have failed to demonstrate benefit.[2] One report[3] examined sympathetic activity across a spectrum of LVEFs in HF and observed that sympathetic activation was present in those with LVEF >35% but did not report specifically on those patients with LVEF >50%. We therefore sought to extend those observations by specifically examining the degree of SNS activation in HFpEF (relative to patients with LVEF <50%) in the ADMIRE-HF trial with the use of iodine-123 meta-iodobenzylguanidine (^{123}I-mIBG) imaging.

ADMIRE-HF was a multicenter study evaluating the prognostic role of cardiac sympathetic innervation imaging with the use of ^{123}I-mIBG in symptomatic HF patients with site-reported LVEFs ≤35%.[4] For quality purposes, echocardiograms were submitted to an independent core laboratory that determined LVEFs, which allowed us to identify a subset of patients who had LVEFs >35%. We stratified subjects based on the core laboratory–adjudicated LVEF: ≤40% for HFrEF, 41%–49% for HF with mid-range LVEF (HFmrEF), and ≥50% for HFpEF. After ^{123}I-mIBG imaging, patients were followed for the end points of all-cause and cardiac death. A total of 884 patients (20.5% female, overall median age 63 years) were included and stratified as follows: 27 (3%) HFpEF, 125 (14%) HFmrEF, and 732 (83%) HFrEF (Supplemental Table). Patients with HFpEF tended to be older (median [interquartile range]: 65 (58–75) vs 63 (55–73) and 62 (54–70) years; $P = .09$ overall), were more likely to be female [44.4% vs 23.2% and 19.1%; $P < .02$ for both comparisons], and tended to have more hypertension (81.5% vs 68.8% [$P = .19$] and 63.7% [$P = .06$]) than patients with HFmrEF and HFrEF. Patients with HFpEF were more symptomatic compared with HFmrEF and HFrEF (New York Heart Association functional class (NYHA) III: 37% vs 12% and 6.8%; $P = .007$). In terms of the ^{123}I-mIBG characteristics, late heart/mediastinum ratio (H/M) was higher in HFpEF compared with HFmrEF and HFrEF (1.58 [1.39–1.77] vs 1.48 [1.35–1.62] and 1.40 [1.29–1.55]; $P < .05$ for both comparisons with HFpEF; Fig. 1). The washout rate was lower in HFpEF compared with HFmrEF and HFrEF (25.79 [16.37–33.45] vs 29.5 2 [22.36–38.67] and 34.46 [26.52–41.64]; $P < .0001$ overall). The plasma level of norepinephrine (pg/mL) was similar among the groups: 582 (474–838) for HFpEF, 592 (366–816) for HFmrEF and 583 (407–832) for HFrEF ($P = .8$ overall comparison).

Patients in this cohort had an extended follow-up for up to 9 years (median 4.4 [1.98–7.23] years). At year 7, 288 patients (32.6%) had reached the end point of all-cause mortality: 242 (33.1%) in HFrEF, 37 (29.6%) in HFmrEF, and 9 (33.3%) in HFpEF ($P = .74$ for overall comparison among groups). Cardiac death occurred in 117 patients (13.2%): 104 (14.2%) in HFrEF, 12 (9.6%) in HFmrEF, and 1 (3.7%) in HFpEF ($P = .12$ for overall comparison among groups). By classifying patients into 2 prespecified groups, late H/M <1.6 and ≥1.6, ^{123}I-mIBG was able to risk-stratify patients with HFrEF and HFmrEF for the outcomes of all-cause mortality and cardiac death. The limited number of patients in the HFpEF group did not allow for the assessment of these hard outcomes in that group.

To our knowledge, this is the first study to specifically characterize the sympathetic activity of HFpEF patients defined by a core laboratory–defined LVEF of >50%. It has been established that abnormal cardiac sympathetic

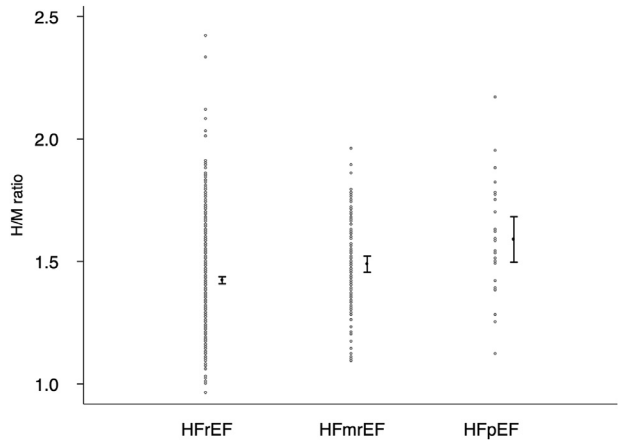

Fig. 1. Late heart/mediastinum ratios (H/M ratios) grouped by HF type. The data points and error bars represent the mean values and 95% confidence intervals. The mean H/M ratio in HFrEF was lower compared with HFmrEF and HFpEF ($P < .05$ for both comparisons). The H/M ratio for HFpEF tended to higher in comparison with compared with HFmrEF ($P = .05$).

innervation is associated with higher morbidity and mortality risk among HFrEF patients. Our findings suggest that patients with HFpEF have comparatively less sympathetic activation than patients with HFmrEF and HFrEF (as suggested by greater myocardial ^{123}I-mIBG uptake) despite more severe HF (eg, greater proportion in NYHA III). Larger studies are needed to assess the role of ^{123}I-mIBG uptake on risk-stratification of hard outcomes in HFpEF patients.

Limitations of this analysis include a small number of patients with LVEF >50%, increased washout rates and similar plasma norepinephrine levels in the HFpEF patients relative to the other groups, and the lack of information regarding concomitant use of beta-blocking agents. However, this study provides an assessment of sympathetic neuronal activity with the use of myocardial ^{123}I-mIBG uptake in HFpEF patients defined by a core laboratory measurement of LVEF >50%. A more complete understanding of the role of sympathetic activation in the pathophysiology in HFpEF is warranted to inform interventions that will be effective in this challenging disorder.

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Disclosures

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.02.014.

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