SUPPLEMENTAL MATERIAL

Table S1. Echocardiographic Characteristics of Study Participants.

Variables	Summary Statistics			P-values (Holm adj.)		
	Control, N = 20*	HFpEF, N = 33*	HFrEF, N = 28*	Control vs. HFpEF	Control vs. HFrEF	HFpEF vs. HFrEF
LV EDV index, mL/m^2	45 (6)	50 (21)	119 (58)	0.68	<0.01	<0.01
LV ESV index, mL/m^2	16 (3)	21 (12)	83 (49)	0.05	<0.01	<0.01
LVEF (Simpson's), %	65 (7)	59 (8)	33 (9)	<0.01	<0.01	<0.01
LV Mass index, mL/m^2	71 (12)	104 (38)	158 (70)	0.02	<0.01	<0.01
LA volume index, mL/m^2	23 (5)	39 (11)	43 (16)	<0.01	<0.01	0.28
Relative wall thickness	0.32 (0.03)	0.34 (0.04)	0.27 (0.07)	0.15	<0.01	<0.01
E/A ratio	1.65 (0.62)	1.35 (0.81)	1.45 (1.06)	0.71	0.90	0.90
E/e' ratio	6.8 (2.0)	11.0 (5.2)	16.4 (5.3)	<0.01	<0.01	<0.01
GLS, % (*-1)	19.5 (2.9)	16.2 (4.0)	8.1 (3.6)	<0.01	<0.01	<0.01

* n (%); Median (IQR); Mean (SD)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LV, left ventricle; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; GLS, global longitudinal strain; E, early diastolic transmitral flow velocity; A, late diastolic transmitral flow velocity; e', early diastolic mitral annular tissue velocity;

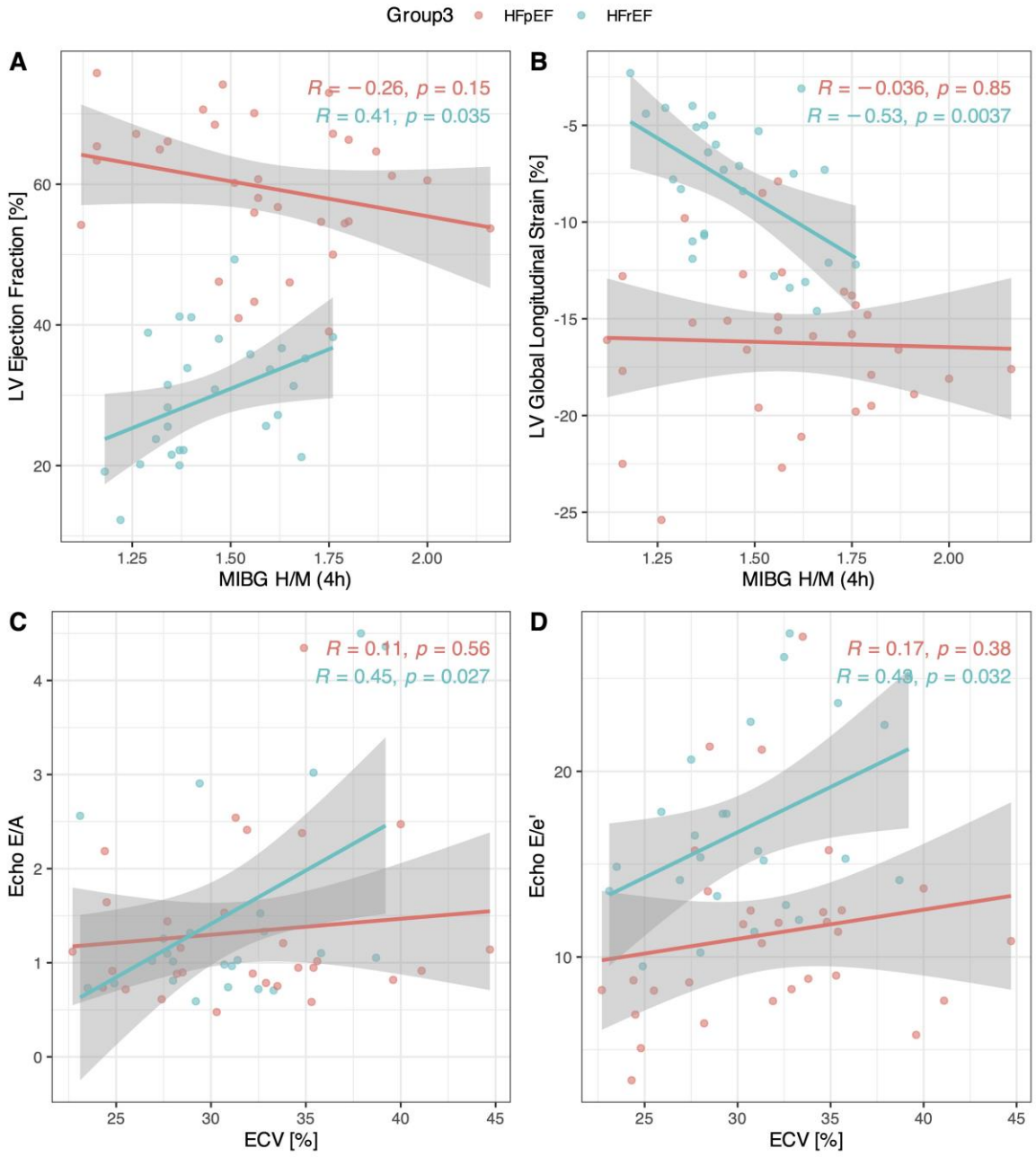
Table S2. Cardiopulmonary Exercise Testing Characteristics of Study Participants.

Variables	Summary Statistics			P-values (Holm adj.)		
	Control, N = 20*	HFpEF, N = 33*	HFrEF, N = 28*	Control vs. HFpEF	Control vs. HFrEF	HFpEF vs. HFrEF
At rest						
Heart rate, bpm	82 (13)	72 (13)	78 (14)	0.05	0.28	0.28
Systolic blood pressure at rest, mmHg	119 (20)	140 (18)	129 (23)	<0.01	0.12	0.08
Diastolic blood pressure at rest, mmHg	79 (9)	89 (11)	83 (13)	0.02	0.34	0.07
During exercise						
Peak heart rate, bpm	163 (18)	127 (27)	135 (27)	<0.01	0.01	0.24
Peak systolic blood pressure, mmHg	172 (26)	187 (29)	166 (24)	0.15	0.41	0.01
Peak diastolic blood pressure, mmHg	86 (11)	91 (14)	81 (11)	0.32	0.32	0.02
Exercise duration, s	774 (160)	534 (126)	719 (212)	0.04	0.41	0.11
Peak RER	1.15 (0.2)	1.01(0.4)	1.00 (0.1)	0.03	0.02	0.29
% predicted peak VO2	103 (25)	86 (26)	78 (19)	0.04	<0.01	0.19
Crude peak VO_2, ml/min	1,972 (687)	1,540 (601)	1,427 (425)	0.03	<0.01	0.45
Peak VO_2, ml/min/kg	30 (10)	19 (6)	18 (4)	<0.01	<0.01	0.58
OUES	1,818 (583)	1,545 (569)	1,397 (503)	0.20	0.04	0.31
Peak oxygen pulse, mL/min/beat	12.3 (3.9)	13.1 (4.4)	11.9 (3.5)	1.00	1.00	0.72
% predicted oxygen pulse	114 (25)	110 (33)	101(31)	0.71	0.53	0.53

* n (%); Median (IQR); Mean (SD)

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; RER, respiratory exchange ratio; VO_2, oxygen uptake; VE, pulmonary ventilation; VCO_2, carbon dioxide production; OUES, oxygen uptake efficiency slope.

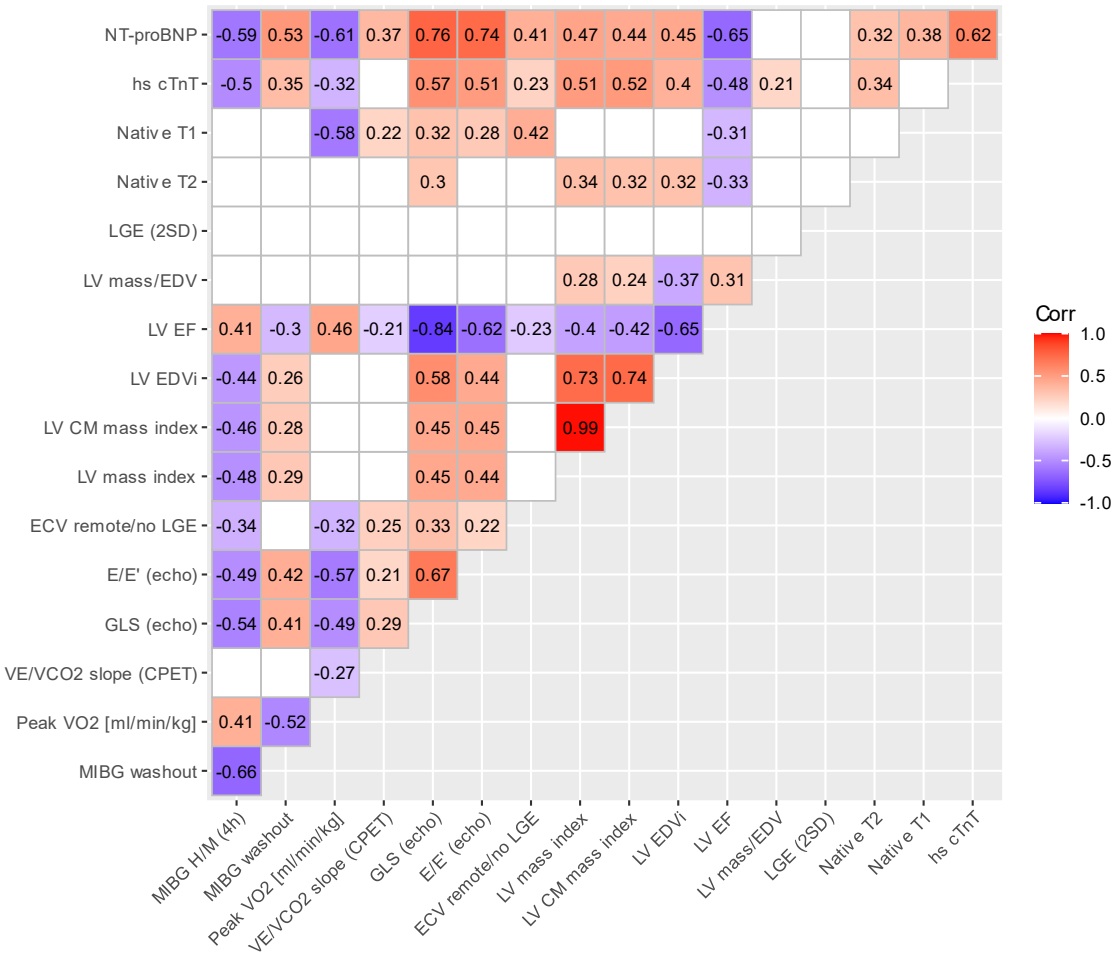
Figure S1: ^{123}I-MIBG H/M and CMR-ECV associations with LV remodeling across study groups



A: The left ventricular ejection fraction (LVEF) correlated significantly (r=0.41; p=0.035) with the MIBG H/M ratio in HF patients with reduced ejection fraction (HFrEF), but not with preserved ejection fraction (HFpEF). B: Similarly, to LVEF, global longitudinal strain

correlated significantly with the MIBG H/M ratio in HF patients with reduced ejection fraction (HFrEF), but not with preserved ejection fraction (HFpEF) C: ECV correlated significantly with the diastolic function index E/A. D: ECV correlated significantly ($r=0.43$; $p=0.032$) with the diastolic function index E/e'. E/e' was significantly higher in HFrEF compared HFpEF, indicating a worse impairment of diastolic function in HFrEF. E/e' correlated only nominally with MIBG H/M in HFrEF.

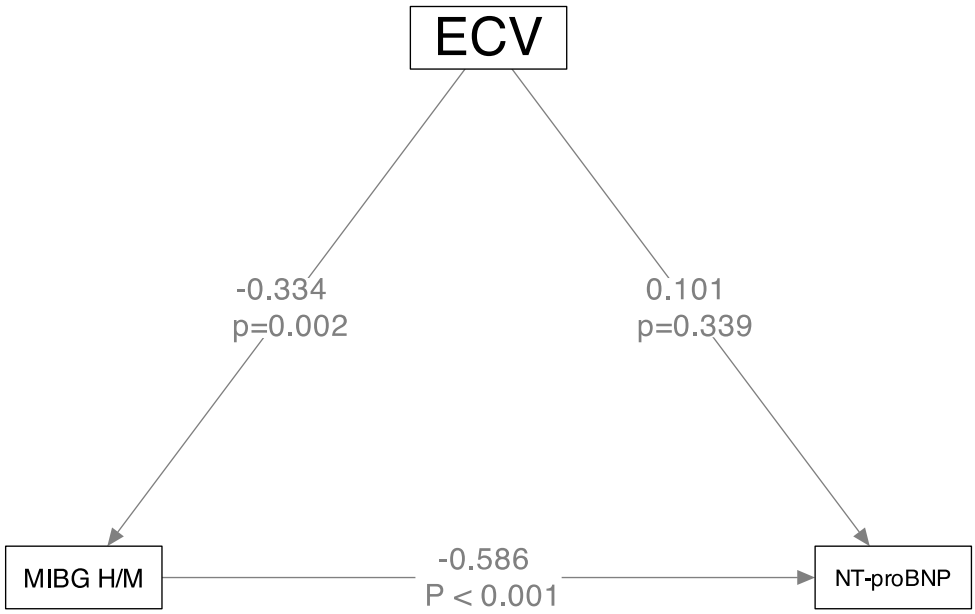
Figure S2: Associations of imaging variables with ^{123}I-MIBG late H/M ratio across all participants:



Several imaging variables demonstrated significant associations with ^{123}I-MIBG late heart-to-mediastinum (H/M) ratio across all participants. Significant correlations (Pearson) with late ^{123}I-MIBG H/M were found for: LVEF (R=0.41, p<0.05), LV end-diastolic volume index (R=-

0.44, p<0.001), LV mass index (R=-0.48, p<0.001), LV cardiomyocyte (CM) mass index (R=-0.46, p<0.001), extracellular volume (ECV) remote (R=-0.34, p<0.003), E/e' (R=-0.49, p<0.001), and global longitudinal strain (GLS) (R=-0.35, p<0.001). Only significant correlations (p<0.05) are depicted in the correlation matrix plot, with the numbers in the cells indicating the strength of Pearson's correlation. For the serum biomarkers cardiac high-sensitivity troponin T (hs-cTnT) and NT-proBNP their log-transformed values were used.

Figure S3: **Medication analysis**:



The effects of the myocardial extracellular volume (ECV; average excluding LGE segments) and ^{123}I-MIBG H/M with NT-proBNP were analyzed with a mediation model that hypothesized that ECV may have a direct effect on NT-proBNP, and also an indirect effect mediated by ^{123}I-MIBG H/M. The myocardial extracellular volume (ECV) had no significant direct effect on NT-proBNP, but the indirect effect mediated by the myocardial ^{123}I-MIBG H/M was significant (P<0.001). The indirect effect mediated by MIBG H/M suggests that the mechanism for the ECV effect on NT-proBNP may involve a reduction of sympathetic innervation density by expansion of the extracellular matrix, a characteristic of adverse tissue remodeling in HF patients.