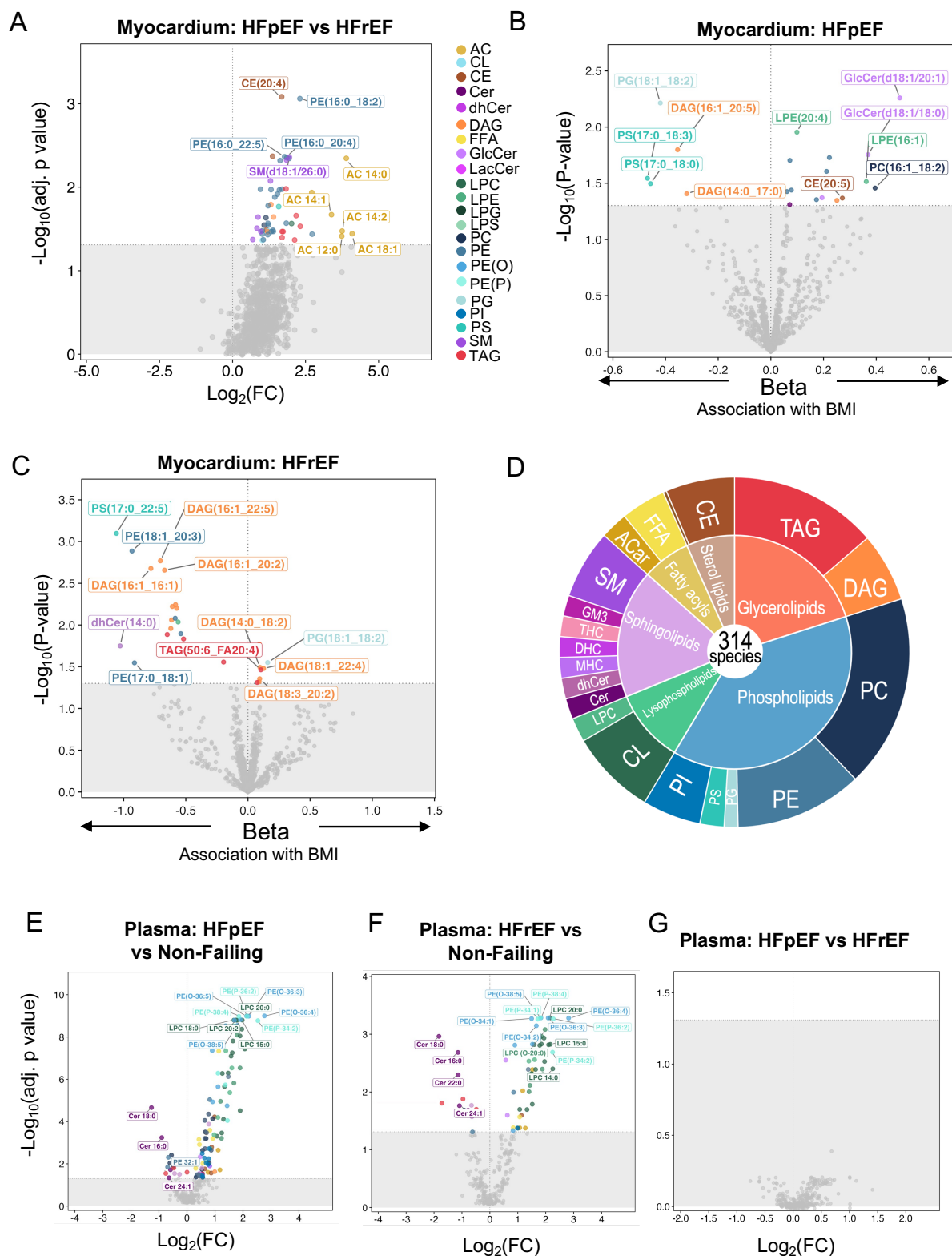


Extended Data
Figures and Tables

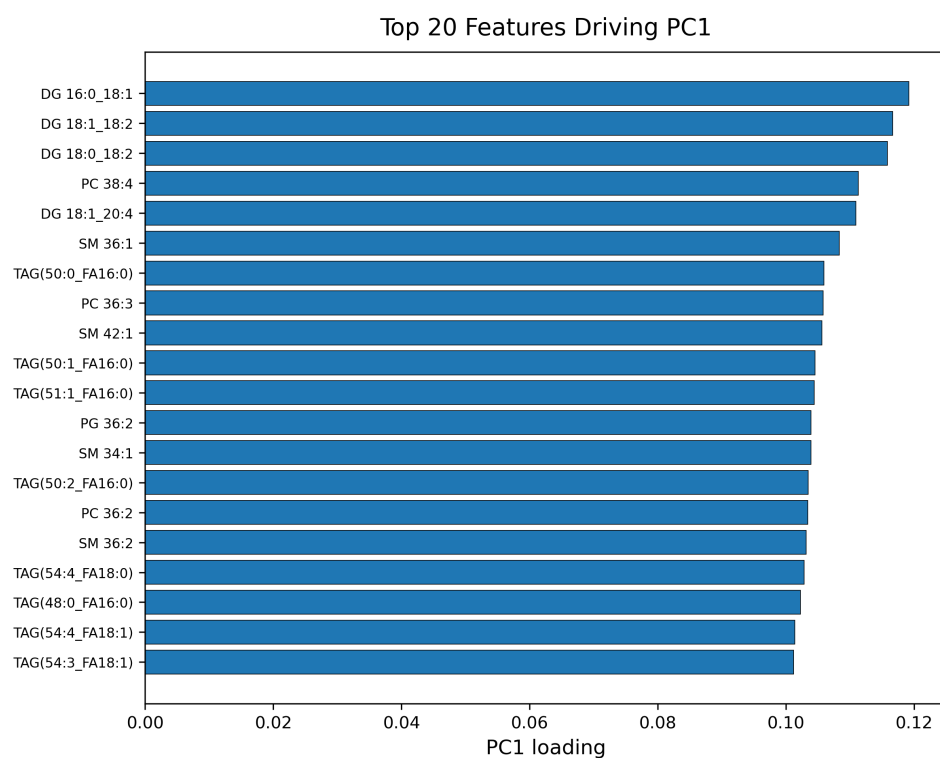
Integrated Myocardial and Plasma Lipidome Landscape Across the Human Obesity–
Heart Failure Spectrum

Polhemus, Butt, et al.

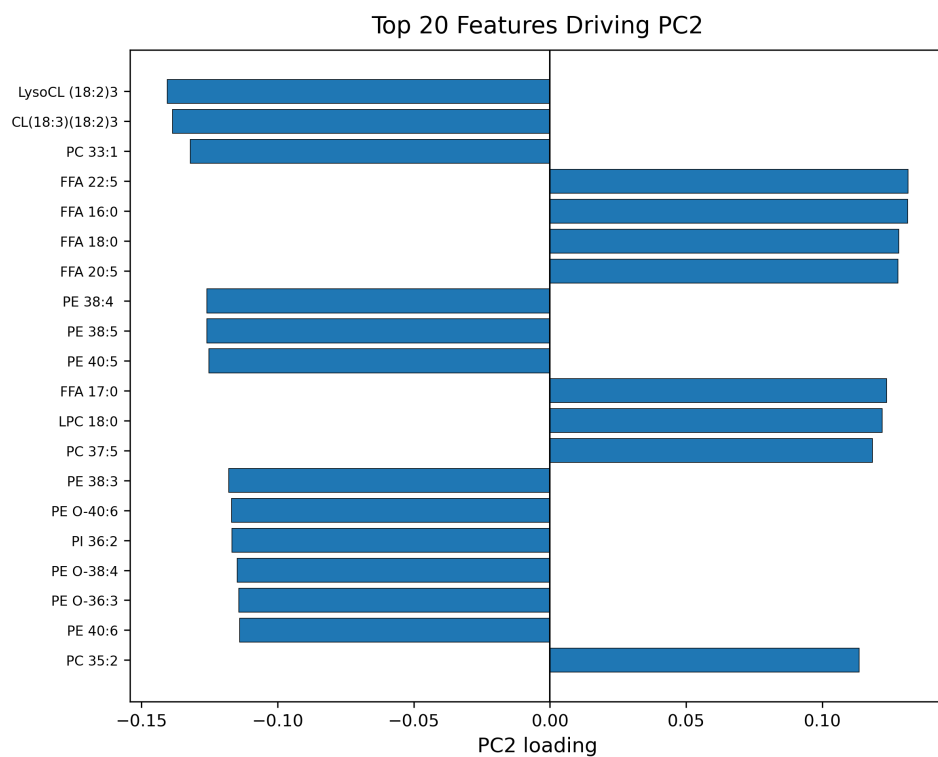


Extended Figure 1. Human plasma and myocardial lipidome comparison in NF, HFpEF, and HFrEF. (a) Volcano plot of the myocardial lipidome of HFpEF versus HFrEF. (b) Volcano plot of BMI as a continuous variable correlated with lipid species abundance in HFpEF myocardium. Species above the horizontal line have slopes significantly different from zero ($p < 0.05$). The x-axis represents the regression coefficient (β) for BMI, where species to the right of the vertical line indicate increasing lipid abundance with higher BMI and species to the left indicate decreasing abundance with higher BMI in HFpEF. (c) Volcano plot of BMI as a continuous variable correlated

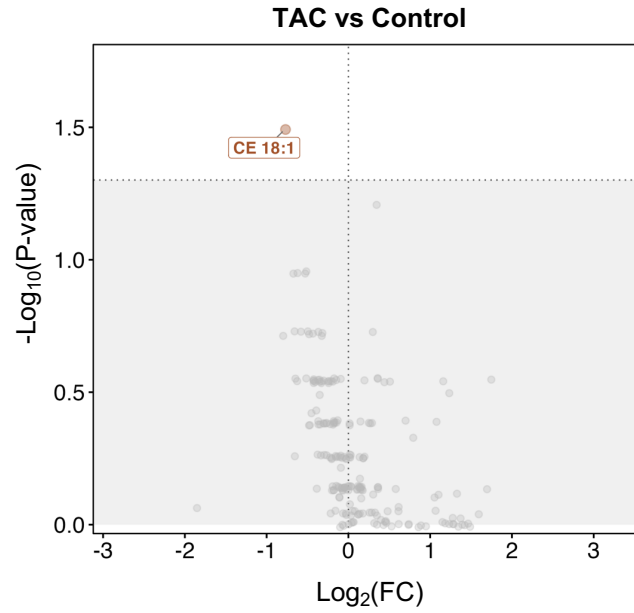
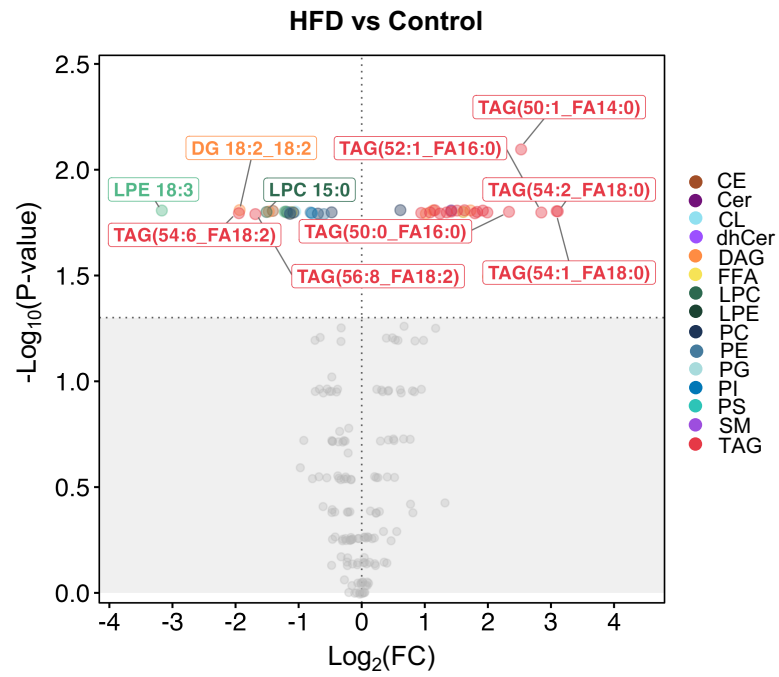
A



B



Extended Figure 3. Leading components for PC1 (A) and PC2 (B) from the PCA plot in Figure 5a comparing lipidomes of human and animal models of obesity and heart failure. Top 20 features for PC1 and PC2 are listed on the y-axis.

A**B**

Extended Figure 4. Animal model myocardial lipidomics. (a) Volcano plot for TAC mouse versus sham. Horizontal dashed line: nominal p-value < 0.05; vertical dashed lines: $\text{log}_2\text{FC}=0$. (b) Volcano plot for high-fat diet mouse (16 weeks) versus control.

EXTENDED TABLES

Extended Table 1. Clinical Characteristics by Study Group, Myocardial Lipidomics

Variable	Non-failing (n=40)	HFpEF (n=29)	HFrEF (n=13)	P value (Overall)	P value HFpEF vs NF	P value HFrEF vs NF	P value HFpEF vs HFrEF
Demographics							
Age, y	54.5	63 (53;72)	51 (49;63)	0.006	0.008	1.000	0.074
Sex, Female	23 (58%)	15 (52%)	4 (31%)	0.245	0.807	0.119	0.317
Race							
Black or African American	6 (15%)	16 (55%)	5 (38%)	0.002	<0.001	0.112	0.505
Hispanic	1 (2%)	0 (0%)	0 (0%)	0.588	1.000	1.000	1.000
White	33 (82%)	13 (45%)	8 (62%)	0.005	0.002	0.140	0.505
Comorbidities							
Hypertension	18 (45%)	25 (86%)	13 (100%)	<0.001	<0.001	<0.001	0.539
Diabetes	9 (22%)	13 (45%)	4 (31%)	0.144	0.064	0.712	0.499
CAD	0 (0%)	11 (38%)	3 (23%)	<0.001	<0.001	0.012	0.481
Atrial fibrillation or flutter	NA	9 (31%)	6 (46%)	NA	NA	NA	0.492
Heart failure hospitalization within 12m	NA	14 (48%)	NA	NA	NA	NA	NA
Medications							
ACEi/ARB	9 (22%)	13 (45%)	9 (69%)	0.007	0.064	0.005	0.200
Beta Blocker	8 (20%)	15 (52%)	13 (100%)	<0.001	0.008	<0.001	0.003
Diuretic	1 (2%)	24 (83%)	13 (100%)	<0.001	<0.001	<0.001	0.288
Lipid lowering therapy	6 (15%)	23 (79%)	6 (46%)	<0.001	<0.001	0.050	0.029
Oral hypoglycemic	5 (12%)	12 (41%)	1 (8%)	0.007	0.009	1.000	0.033
Insulin	3 (8%)	6 (21%)	2 (15%)	0.277	0.146	0.586	1.000
Vitals & Anthropometrics							
BMI, kg/m ²	29.9	37.3 (31;41)	26 (24.6;27.9)	<0.001	0.019	0.247	<0.001
HR, bpm	NA	80.5	NA	NA	NA	NA	NA
SBP, mmHg	NA	136.5 (119.5;148)	NA	NA	NA	NA	NA
DBP, mmHg	NA	72	NA	NA	NA	NA	NA
Echocardiography							
LVEF, %	60 (60;65)	65 (60;70)	15 (10;20)	<0.001	0.804	<0.001	<0.001
LVEDD, cm	4.4 (4.0;4.8)	4.4 (4.0;4.8)	7.3 (6.1;7.6)	<0.001	1.000	<0.001	<0.001
LVMI	NA	80.2 (69.8;100.3)	NA	NA	NA	NA	NA
E/e'	NA	11.9	NA	NA	NA	NA	NA
Biomarkers							
NT-proBNP, mg/mL	NA	179 (113;454)	NA	NA	NA	NA	NA
A1c, %	NA	6.1 (5.6;8)	NA	NA	NA	NA	NA
LDL, mg/dL	NA	85 (65;106)	NA	NA	NA	NA	NA
HDL, mg/dL	NA	47 (39;55)	NA	NA	NA	NA	NA
Triglycerides, mg/dL	NA	105	NA	NA	NA	NA	NA
Creatinine, mg/dL	0.9 (0.7;1.4)	1.2 (1;1.9)	NA	NA	0.018	NA	NA
eGFR, mL/min/1.73m ²	77.6 (57.8;103.4)	55.1 (36.4;66.9)	NA	NA	0.005	NA	NA

Hemodynamics (HFpEF vs HFrEF only)							
Right atrial pressure	NA	8 (5;12)	11 (7;14)	NA	NA	NA	0.137
PASP, mmHg	NA	33.5	47 (45;56)	NA	NA	NA	0.017
PADP, mmHg	NA	18 (12;25.2)	22 (16;29)	NA	NA	NA	0.457
PCWP, mmHg	NA	17 (10;25)	23 (17;25)	NA	NA	NA	0.113
Cardiac index	NA	2.3 (1.9;2.6)	2 (1.8;2.8)	NA	NA	NA	0.687
6MWT, m	NA	335.3 (123;426.7)	NA	NA	NA	NA	NA
HFrEF Etiology (HFrEF only)							
Familial	NA	NA	3 (23%)	NA	NA	NA	NA
Ischemic	NA	NA	3 (23%)	NA	NA	NA	NA
LV noncompaction	NA	NA	1 (8%)	NA	NA	NA	NA
Nonischemic	NA	NA	5 (38%)	NA	NA	NA	NA
Sarcoidosis	NA	NA	1 (8%)	NA	NA	NA	NA

Data presented as median (25th;75th percentile) for continuous variables or n (%) for categorical variables. Continuous variables: Kruskal-Wallis test (3 groups) with Dunn post-hoc test (Bonferroni-corrected) or Mann-Whitney U test (2 groups). Categorical variables: Fisher exact test (pairwise) or χ^2 test (overall 3-group). NA = data not available. Abbreviations:ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; LDL = low-density lipoprotein; HDL = high-density lipoprotein; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NF = non-failing; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PADP = pulmonary artery diastolic pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; 6MWT = 6-minute walk test.

Extended Table 2. Clinical Characteristics by Study Group, Plasma lipidomics cohort

Variable	Non-failing (n=12)	HFpEF (n=37)	HFrEF (n=8)	P value (Overall)	P value HFpEF vs NF	P value HFrEF vs NF	P value HFpEF vs HFrEF
Demographics							
Age, y	59.5 (55;63.2)	67 (57;72)	54.5 (48;63.2)	0.059	0.103	0.562	0.047
Sex; Female	6 (50%)	24 (65%)	0 (0%)	0.004	0.498	0.042	<0.001
Race							
Black or African American	1 (8%)	18 (49%)	4 (50%)	0.039	0.017	0.109	1.000
Hispanic	0 (0%)	0 (0%)	0 (0%)	NA	1.000	1.000	1.000
White	11 (92%)	18 (49%)	4 (50%)	0.028	0.016	0.109	1.000
Comorbidities							
Hypertension	8 (67%)	32 (86%)	8 (100%)	0.110	0.195	0.117	0.568
Diabetes	1 (8%)	15 (41%)	3 (38%)	0.116	0.073	0.255	1.000
CAD	0 (0%)	6 (16%)	2 (25%)	0.234	0.314	0.147	0.618
Atrial fibrillation or flutter	1 (8%)	14 (38%)	3 (38%)	0.149	0.075	0.255	1.000
Heart failure	0 (0%)	15 (41%)	0 (0%)	0.004	0.010	1.000	0.038
Medications							
ACEi/ARB	3 (25%)	16 (43%)	6 (75%)	0.087	0.323	0.065	0.135
Beta Blocker	3 (25%)	16 (43%)	8 (100%)	0.003	0.323	0.001	0.004
Diuretic	0 (0%)	31 (84%)	8 (100%)	<0.001	<0.001	<0.001	0.572
Lipid lowering therapy	2 (17%)	21 (57%)	4 (50%)	0.053	0.021	0.161	1.000
Oral hypoglycemic	1 (8%)	10 (27%)	1 (12%)	0.314	0.252	1.000	0.657
Insulin	0 (0%)	6 (16%)	2 (25%)	0.234	0.314	0.147	0.618
Vitals & Anthropometrics							
BMI, kg/m ²	24.3 (21.5;29.5)	37.6 (30.3;45.1)	26.1 (24.8;27.3)	<0.001	<0.001	0.734	0.002
HR, bpm	—	74.5 (65;86.8)	—	NA	NA	NA	NA
SBP, mmHg	—	138 (125;158)	—	NA	NA	NA	NA
DBP, mmHg	—	73 (66;81)	—	NA	NA	NA	NA
Echocardiography							
LVEF, %	65 (60;65)	65 (60;66.2)	16 (13.8;18.1)	<0.001	0.918	<0.001	<0.001
LVEDD, cm	3.9 (3.9;4)	4.5 (4.1;5)	7.4 (6.3;7.7)	<0.001	0.006	<0.001	<0.001
LVMI, g/m ²	—	85 (76.0;109.5)	—	NA	NA	NA	NA
E/e'	—	12.9 (9.5;15.4)	—	NA	NA	NA	NA
Biomarkers							
NT-proBNP, pg/mL	—	392 (126;928)	—	NA	NA	NA	NA
HbA1c, %	—	6 (5.5;6.7)	—	NA	NA	NA	NA
LDL, mg/dL	—	81 (58.5;101.5)	—	NA	NA	NA	NA
HDL, mg/dL	—	51 (43;63.5)	—	NA	NA	NA	NA
Triglycerides, mg/dL	—	99 (66.5;147)	—	NA	NA	NA	NA
Creatinine, mg/dL	0.8 (0.7;0.9)	1.1 (0.8;1.5)	1.4 (1.1;1.7)	0.035	0.031	0.037	0.240
eGFR, mL/min/1.73m ²	95.5 (72.2;108.1)	57.8 (43.9;79.2)	61.1 (45.7;75.9)	0.075	0.025	0.146	0.870

Hemodynamics (HFpEF and HFrEF only)							
Right atrial pressure,	NA	9 (7;12)	11.5	NA	NA	NA	0.387
PASP, mmHg	NA	36 (32;45)	46 (43.5;55.5)	NA	NA	NA	0.027
PADP, mmHg	NA	20 (15;25)	23.5 (16.8;26.2)	NA	NA	NA	0.634
PCWP, mmHg	NA	18 (13;22)	23 (17.2;26)	NA	NA	NA	0.246
Cardiac index, L/min/m ²	NA	2.5 (2.2;3.1)	2.2 (2;2.5)	NA	NA	NA	0.117
6MWT, m	NA	258.5 (184.1–385.8)	—	NA	NA	NA	NA
HFrEF Etiology (HFrEF only)							
Ischemic	NA	NA	2 (25%)	NA	NA	NA	NA
Nonischemic	NA	NA	4 (50%)	NA	NA	NA	NA
LV noncompaction	NA	NA	1 (12%)	NA	NA	NA	NA
Sarcoidosis	NA	NA	1 (12%)	NA	NA	NA	NA

Data presented as **median (25th;75th percentile)** for continuous variables or n (%) for categorical variables. Continuous variables: Kruskal-Wallis test (3 groups) with Mann-Whitney U pairwise comparisons. Categorical variables: Fisher's exact test (pairwise) or χ^2 test (overall 3-group). Blank cells indicate data not available for that group. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NA, data not available; NF, non-failing; NICM, non-ischaemic cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; 6MWT, 6-minute walk test.

Extended Table 3. Patient Characteristics by BMI Group — Non-failing cohort

Variable	BMI < 35 (n=26)	BMI ≥ 35 (n=14)	P value
Demographics			
Age, y	54.5 (39.0;63.0)	55.5 (47.2;60.2)	1.000
Sex, Female	16 (62%)	7 (50%)	0.521
Race			
Black or African American	3 (12%)	3 (21%)	0.646
Hispanic	0 (0%)	1 (7%)	0.350
White	23 (88%)	10 (71%)	0.214
Comorbidities			
Hypertension	13 (50%)	5 (36%)	0.510
Diabetes	4 (15%)	5 (36%)	0.234
CAD	0 (0%)	0 (0%)	1.000
Medications			
ACEi/ARB	5 (19%)	4 (29%)	0.694
Beta Blocker	5 (19%)	3 (21%)	1.000
Diuretic	0 (0%)	1 (7%)	0.350
Lipid lowering therapy	3 (12%)	3 (21%)	0.646
Oral hypoglycemic	2 (8%)	3 (23%)	0.310
Insulin	1 (4%)	2 (14%)	0.276
BMI, kg/m²	25.2 (21.9;29.6)	39.7 (37.1;47.2)	<0.001
Echocardiography			
LVEF, %	60.0 (60.0;65.0)	65.0 (60.0;65.0)	0.441
LVEDD, cm	4.0 (3.9;4.6)	4.6 (4.2;4.9)	0.202
Biomarkers			
Creatinine, mg/dL	0.8 (0.7;1.1)	1.2 (0.8;2.0)	0.190
eGFR, mL/min/1.73m ²	85.7 (62.0;105.1)	72.2 (42.7;100.2)	0.372

Non-failing group only. **Data presented as median (25th;75th percentile)** for continuous variables or n (%) for categorical variables. Mann-Whitney U test for continuous variables; Fisher exact test for categorical variables. NA = data not available. Significant p-values (< 0.05) are highlighted in red. Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HR = heart rate; LDL = low-density lipoprotein; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; NA = data not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PADP = pulmonary artery diastolic pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; 6MWT = 6-minute walk test.