

Galectin-3 Is Associated With Stage B Metabolic Heart Disease and Pulmonary Hypertension in Young Obese Patients

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Background—Obesity is a precursor to heart failure with preserved ejection fraction. Biomarkers that identify preclinical metabolic heart disease (MHD) in young obese patients would help identify high-risk individuals for heart failure prevention strategies. We assessed the predictive value of GAL3 (galectin-3), FSTL3 (follistatin-like 3 peptide), and NT-proBNP (N-terminal pro-B-type natriuretic peptide) to identify stage B MHD in young obese participants free of clinically evident cardiovascular disease.

Methods and Results—Asymptomatic obese patients (n=250) and non-obese controls (n=21) underwent echocardiographic cardiac phenotyping. Obese patients were classified as MHD positive (MHD-POS; n=94) if they had abnormal diastolic function or left ventricular hypertrophy and had estimated pulmonary artery systolic pressure ≥ 35 mm Hg. Obese patients without such abnormalities were classified as MHD negative (MHD-NEG; n=52). Serum biomarkers timed with echocardiography. MHD-POS and MHD-NEG individuals were similarly obese, but MHD-POS patients were older, with more diabetes mellitus and metabolic syndrome. Right ventricular coupling was worse in MHD-POS patients ($P < 0.001$). GAL3 levels were higher in MHD-POS versus MHD-NEG patients (7.7 ± 2.3 versus 6.3 ± 1.9 ng/mL, respectively; $P < 0.001$). Both GAL3 and FSTL3 levels correlated with diastolic dysfunction and increased pulmonary artery systolic pressure but not with left ventricular mass. In multivariate models including all 3 biomarkers, only GAL3 remained associated with MHD (odds ratio: 1.30; 95% CI, 1.01–1.68; $P = 0.04$).

Conclusions—In young obese individuals without known cardiovascular disease, GAL3 is associated with the presence of preclinical MHD. GAL3 may be useful in screening for preclinical MHD and identifying individuals with increased risk of progression to obesity-related heart failure with preserved ejection fraction. (*J Am Heart Assoc.* 2019;8:e011100. DOI: 10.1161/JAHA.118.011100.)

Key Words: echocardiography • obesity • prevention • remodeling heart failure

Metabolic heart disease (MHD), a cardiomyopathy characterized by left ventricular hypertrophy (LVH) and/or diastolic dysfunction in the setting of preserved ejection fraction, is common in young obese individuals, with a prevalence ranging from 15% to 56%.¹ The high frequency of MHD in this population is noteworthy for 2 main reasons. First, the prevalence of obesity is steadily rising in the United States, with current estimates at 40% in 2014.² Second, obesity and metabolic syndrome are important precursors to

heart failure with preserved ejection fraction (HFpEF), a major public health concern burdening our healthcare system with significant morbidity, mortality, and cost.^{3,4}

Heart failure (HF) is a progressive disorder, classified by the American College of Cardiology/American Heart Association (ACC/AHA) into 4 stages (A, B, C or D); stage B represents structural heart disease in the absence of clinical signs or symptoms of HF.⁵ Diastolic dysfunction, LVH, and pulmonary hypertension (PH) are preclinical

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Accompanying Tables S1 through S6 and Figure S1 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011100>

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Clinical Perspective

What Is New?

- Obesity is a precursor to heart failure with preserved ejection fraction; metabolic heart disease, a cardiomyopathy characterized by left ventricular hypertrophy and/or diastolic dysfunction, is common in young obese individuals.
- In this study, GAL3 (galectin-3) independently associated with metabolic heart disease, subclinical stage B heart failure enriched with pulmonary hypertension, in young obese individuals.

What Are the Clinical Implications?

- This study suggests biomarkers may help us identify preclinical heart failure and asymptomatic pulmonary hypertension in high-risk individuals with obesity and could serve as a screening biomarker to initiate preventative strategies for heart failure with preserved ejection fraction, including echocardiographic screening and therapy initiation.

echocardiographic abnormalities that precede clinical HF in individuals with stage B MHD.^{6–8} However, given the magnitude of the population at risk for MHD, the widespread use of echocardiography as a screening tool is neither practical nor cost effective. Inexpensive and convenient screening measures that can identify and mechanistically link to stage B MHD would help prioritize and monitor high-risk individuals for further assessment and early intervention.⁹

BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-B-type natriuretic peptide) are biomarkers that are useful in the identification of stage B HF.¹⁰ However, both BNP and NT-proBNP levels are depressed in obesity¹¹ and tend to be lower in HFpEF^{12,13} compared with HF with reduced ejection fraction, thus severely limiting their utility in this population. FSTL3 (follistatin-like 3 peptide), similar to natriuretic peptides, is a cardiomyokine that is upregulated by hypertrophic stimuli¹⁴ with increased circulating levels in HF with reduced ejection fraction.¹⁵ Although FSTL3 has not been evaluated in HF and obesity, it may provide an alternative to natriuretic peptides in this setting. GAL3 (galectin-3) is elevated in symptomatic patients with HF with reduced ejection fraction or HFpEF,¹⁶ but little is known about its ability to identify preclinical stage B HF of any etiology or to identify MHD in the setting of obesity. Accordingly, our goal was to determine whether NT-proBNP, FSTL3, or GAL3 was associated with preclinical MHD in obese participants. Stage B MHD was specifically defined as (1) the presence of increased left ventricular (LV) mass and/or diastolic dysfunction function that is (2) accompanied by PH, as elevated pulmonary pressure is a well-established prognosticator and often portends hemodynamically important LV disease.^{6,17,18}

Methods

The data that support the findings of this study are available from the corresponding author (D.M.G.) on reasonable request.

Study Population

Patients with obesity (n=250) were recruited from outpatient clinics at Boston Medical Center. Obesity was defined as a body mass index (BMI; calculated as kg/m²) ≥30. Nonobese volunteer controls with BMI <30 and no major comorbidities (n=44) were also recruited from Boston Medical Center. All participants with clinically recognized cardiovascular disease (HF, PH, coronary artery disease, valvular disease, angina, or atrial fibrillation), incidental asymptomatic LV systolic dysfunction (LV ejection fraction <50% on echocardiogram), or significant pulmonary disease were excluded. Of the 250 obese patients, 19 were excluded for missing or inadequate echocardiographic data (for the primary analysis), leaving 231 evaluable participants. Of the 44 control participants, 23 with evidence of asymptomatic echocardiographic abnormalities (incident valvular disease, diastolic abnormalities, LVH, or PH) or missing data were excluded from the analysis.

Categorization of MHD Disease

Primary analysis

For the primary analysis, MHD status classification of obese participants was based on the presence or absence of diastolic dysfunction, LVH, and PH. To be classified as *MHD positive* (MHD-POS), a participant needed (1) to have diastolic dysfunction or LVH and (2) to have PH. Obese participants without diastolic dysfunction, LVH, or PH were classified as *MHD negative* (MHD-NEG). Obese participants with PH, LVH, and/or diastolic dysfunction but not meeting criteria for MHD-POS were classified as *indeterminate*. Of the 231 evaluable obese participants, 94 classified as MHD-POS, 52 as MHD-NEG, and 85 as indeterminate (Figure 1A).

Diastolic dysfunction was classified using the updated 2016 American Society of Echocardiography (ASE) guidelines on evaluation of LV diastolic dysfunction.¹⁹ Because of the high percentage of incomplete or absent tricuspid regurgitation jets in this cohort, tricuspid regurgitation velocity was replaced by pulmonary artery systolic pressure (PASP) calculated from pulmonary artery acceleration time (PAAT) using a value of ≥31 mm Hg—a value equivalent to the tricuspid regurgitation velocity requirement in the ASE criteria. LVH was classified as *present* if the LV mass (indexed to height^{2.7}) was ≥45 g/m^{2.7} in women and ≥49 g/m^{2.7} for men.²⁰ PH was

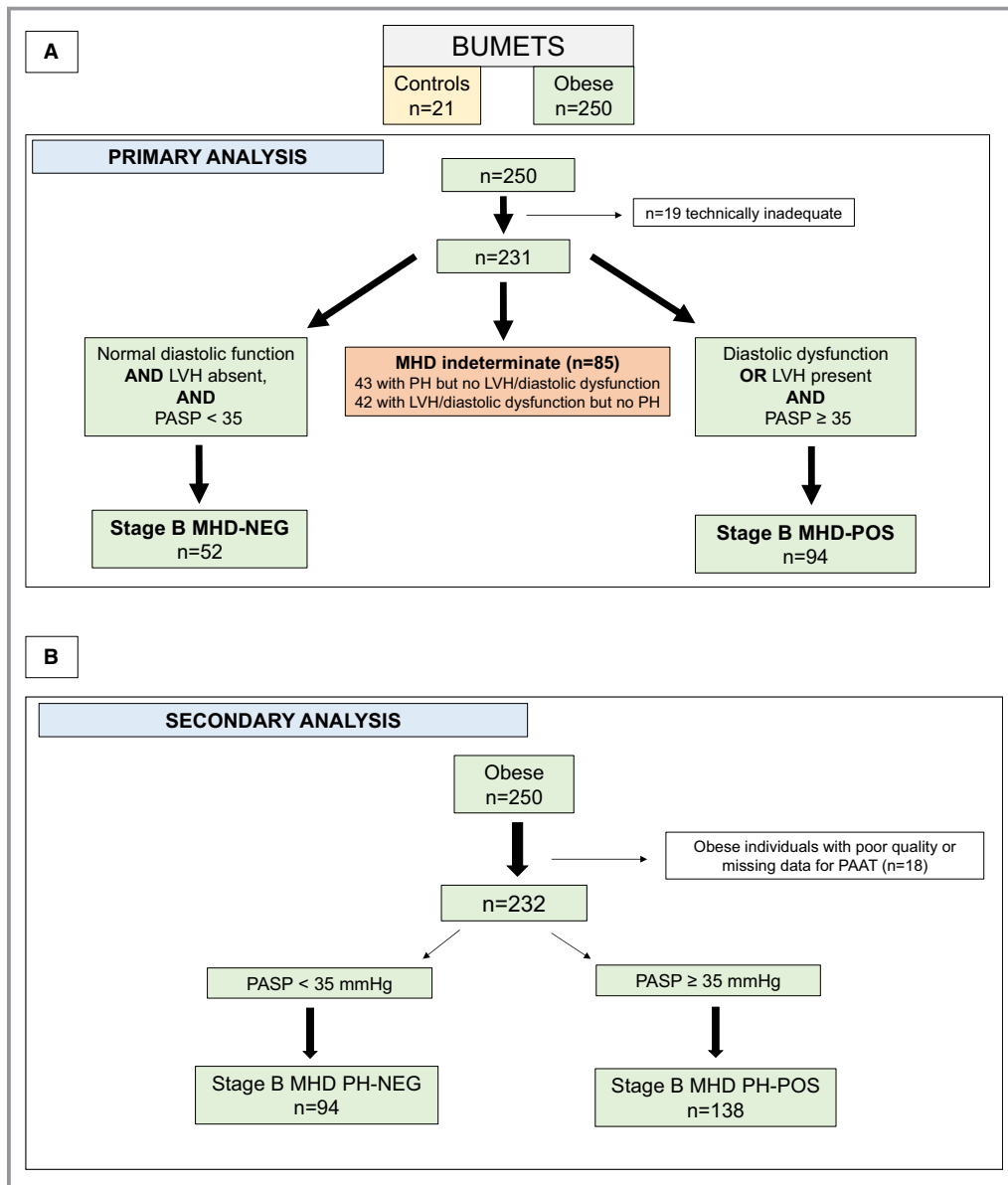


Figure 1. Flow diagram of the classification system of stage B MHD. **A**, Primary analysis used presence of diastolic dysfunction, LVH, and PH for classification of MHD. **B**, Secondary analysis used PH as the sole criterion for MHD presence. BUMETS indicates Boston University Metabolic Heart Disease Study; LVH, left ventricular hypertrophy; MHD, metabolic heart disease; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; PAAT, pulmonary artery acceleration time; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension.

classified as *present* if the estimated PASP derived from PAAT was ≥ 35 mm Hg.¹⁷

Secondary analysis

In a secondary analysis, obese participants were classified as PH-POS if the estimated PASP derived from PAAT was ≥ 35 mm Hg and as PH-NEG if PASP was < 35 mm Hg. For this analysis, 18 patients were excluded for inadequate quality of the pulse-wave Doppler signal from the right ventricular

(RV) outflow tract, leaving 232 evaluable participants (93%) for analysis.

Clinical Assessment

A comprehensive medical history and physical examination were performed for all participants. Fasting laboratory values, resting heart rate, blood pressure (obtained after 10 minutes resting in a sitting position, averaged over 3 consecutive

measurements), and anthropometrics were obtained for all patients. Diabetes mellitus was defined as fasting blood glucose level ≥ 126 mg/dL and/or active medical therapy with an oral hypoglycemic agent and/or insulin. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, and/or current antihypertensive therapy. Metabolic syndrome was defined as meeting ≥ 3 of the following 5 criteria: (1) increase waist circumference (≥ 102 cm for men or ≥ 88 cm for women), (2) increased fasting triglycerides (≥ 150 mg/dL), (3) high blood pressure ($\geq 130/85$ mm Hg or antihypertensive therapy), (4) decreased high-density lipoprotein cholesterol (< 40 mg/dL in men, < 50 mg/dL in women), (5) impaired fasting glucose (≥ 100 mg/dL).²¹ Ideal body weight was calculated using the following equation: $a + (2.3)([\text{height in inches}] - 60)$, where $a = 50$ kg for men and $a = 45.5$ kg for women.²² The Boston University Medical Center institutional review board approved this study, and all participants provided informed consent before study enrollment.

Assessment of Cardiac Structure and Function

Two-dimensional transthoracic echocardiograms using a 1- to 5-MHz transducer and commercially available ultrasound machine (iE33; Phillips Medical Systems) was used by a single experienced sonographer (A.P.). Echocardiograms were interpreted offline in a blinded manner. Standard echocardiographic analysis was applied according to published recommendations.²³ LV mass was calculated utilizing the cubed method with an index applying height to the power of 2.7 to account for body habitus in our obese cohort.²⁴ LV diastolic function included pulse-wave Doppler assessment of early (E) and late (A) transmitral inflow velocities, E/A ratio, E-wave deceleration time, and tissue Doppler imaging of myocardial velocities averaging both the medial and lateral mitral annulus.¹⁹ LV filling pressure estimation, utilizing the mitral E wave and tissue Doppler mean e' velocity as a ratio, was calculated as described previously.¹⁹

Right heart assessment was performed according to published recommendations for right atrial area and RV basal diameter.²⁵ Tricuspid annular plane systolic excursion (TAPSE) was obtained by placing an M-mode cursor on the lateral tricuspid annulus in an apical 4-chamber view and capturing maximal annular movement during systole. Utilizing pulse-wave Doppler interrogation of the pulmonary artery ejection, PAAT was measured as the time interval from the onset to peak flow velocity of pulmonary artery flow. RV ejection was the total time interval from onset to the cessation of pulmonary artery flow. PASPs were estimated from PAAT using a previously validated equation: $10^{((-0.004 \times \text{PAAT}) + 2.1)}$.²⁶

All echocardiographic measurements were averaged over 3 consecutive cardiac cycles (when available).

Echocardiographic measurements were performed by 2 trained cardiologists (D.M.G. and Y.W.) with repeated measurements of 10 scans showing an intraobserver coefficient of variation of 1.6% to 6.1% and an interobserver coefficient of variation of 1.8% to 7.0% for linear measurements. The intraobserver coefficient of variation was 7.3% with intraclass correlation coefficients ranging from 92% to 96%.

Biochemical Measurements

Following an overnight fast, blood samples were obtained from study participants the next morning. The citrated plasma samples were centrifuged immediately and stored at -80°C until assayed. No freeze-thaw cycles were performed before the assays described below. NT-proBNP, GAL3, and FSTL3 levels were determined using ELISA kits. Assay calibration was performed according to the manufacturer's recommendations, with values normalized to a standard curve. Other biochemical testing including total cholesterol, HDL (high-density lipoprotein), triglyceride, and creatinine concentrations were determined using standard clinical laboratory methods at Boston Medical Center. Estimated glomerular filtration rate (eGFR) was determined by the Chronic Kidney Disease Epidemiology Collaboration formula: $\text{eGFR (mL/min/1.73m}^2) = 141 \times \min(\text{serum creatinine}/\kappa, 1)^{\alpha} \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.159$ (if black); κ is 0.7 (females) and 0.9 (males) and α is -0.329 (females) and -0.411 (males).²⁷

Statistical Analysis

Baseline characteristics and echocardiographic data were reported as mean \pm SD, median (interquartile range), or number (percentage) unless otherwise specified. Between-group differences were compared using 1-way ANOVA, Kruskal-Wallis, or χ^2 analysis with Bonferroni correction for multiple-comparison testing (P values considered statistically significant at $< 0.05/3 = 0.02$) for between-group comparisons. Natural logarithm transformations were applied to FSTL3 and NT-proBNP levels for analyses to normalize right-skewed distributions. Correlation testing for biomarkers and echocardiographic and clinical characteristics used pairwise Pearson correlation coefficients. Multivariate linear regression models were used to explore relationships between echocardiographic parameters and clinical characteristics. Univariate logistic regression models using MHD-POS as the outcome of interest were applied to clinical and echocardiographic variables to determine associations. Variables that were significant ($P < 0.01$) were subsequently applied in fully adjusted multivariate models to prevent model overfitting. All analyses were performed using SAS 9.3 (SAS Institute).

Results

Participant Characteristics

MHD-POS and MHD-NEG participants were similar in body weight, BMI, and body surface area, with 40% of all obese patients qualifying for class 3 obesity with a BMI ≥ 40

(Table 1). Control participants had a mean BMI of 25 with no diabetes mellitus, hypertension, or metabolic syndrome. MHD-POS participants were older with a higher prevalence of comorbidities including diabetes mellitus, hypertension, hyperlipidemia, and metabolic syndrome than MHD-NEG participants. Likewise, MHD-POS (versus MHD-NEG) participants were more likely to be receiving

Table 1. Baseline Characteristics

	Nonobese Controls (n=21)	Obese MHD-NEG (n=52)	Obese MHD-POS (n=94)	P Value
Age, y	43±12	36±11	47±9*	<0.001
Female, n (%)	18 (86)	47 (90)	69 (73)	0.04
Black, n (%)	9 (43)	34 (65)	61 (65)	0.15
Anthropometrics				
Height, m	167±6	166±9	166±10	0.70
Ideal body weight, kg	60±6	58±8	59±9	0.68
Actual body weight, kg	69±8	103±22 [†]	109±22 [†]	<0.001
Body mass index, kg/m ²	25±3	37±7 [†]	40±8 [†]	<0.001
Body surface area, m ²	1.8±0.1	2.1±0.2 [†]	2.1±0.2 [†]	<0.001
Waist circumference, cm	82±9	113±18 [†]	119±16 [†]	<0.001
Comorbidities, n (%)				
Diabetes mellitus	0 (0)	6 (12)	37 (39)	<0.001
Hypertension	0 (0)	16 (31)	60 (64)	<0.001
Current smoking	1 (4)	4 (8)	13 (14)	0.45
Obstructive sleep apnea	0 (0)	6 (12)	20 (21)	0.02
Hyperlipidemia	1 (5)	14 (27)	50 (53)	<0.001
Metabolic syndrome	0 (0)	28 (54)	79 (84)	<0.001
Medications, n (%)				
ACEI or ARB	0 (0)	8 (15)	43 (46)	<0.001
β-Blocker	0 (0)	4 (8)	23 (24)	0.002
Oral hypoglycemic agent	0 (0)	6 (12)	26 (28)	0.002
Insulin	0 (0)	1 (2)	15 (16)	0.007
Laboratory values				
Total cholesterol, mg/dL	184 (178–217)	182 (157–210)	188 (165–206)	0.85
HDL, mg/dL	61 (52–67)	45 (39–53) [†]	45 (39–53) [†]	<0.001
Triglycerides, mg/dL	60 (48–84)	100 (70–151)	117 (82–176) [†]	0.008
Triglyceride/HDL ratio	1.1 (0.7–1.6)	2.5 (1.3–3.3)	2.7 (1.8–4.0) [†]	0.001
eGFR, mL/min/1.73 m ²	99±16	128±25 [†]	122±28 [†]	<0.001
Biomarkers				
NT-proBNP, pmol/L	420 (279–736)	554 (431–684)	607 (485–773)	0.36
GAL3, ng/mL	5.7±1.6	6.3±1.9	7.7±2.3* [†]	<0.001
FSTL3, pg/mL	4665 (3976–5951)	5335 (4414–6970)	5768 (4477–7521)	0.02

Data are mean±SD, median (interquartile range), or n (%). P value reflect overall group differences. P value listed reflects ANOVA comparison across all 3 groups; symbols denote between group comparisons with Bonferonni correction. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; FSTL3, follistatin-like 3 peptide; GAL3, galectin-3; HDL, high-density lipoprotein; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*P<0.02 vs obese MHD-NEG participants.

[†]P<0.02 vs controls.

hypertensive therapy and hypoglycemic medications (oral or insulin therapy). MHD-indeterminate participants, who were excluded from the primary analysis (n=85), were generally similar to MHD-POS and MHD-NEG participants regarding comorbidities and echocardiographic variables (Table S1).

Cardiac Structure and Function

As expected given the grouping criteria, MHD-POS (versus MHD-NEG) participants had higher LV mass and higher mean PASP (48±9 versus 27±4 mm Hg, respectively; Table 2). In addition, MHD-POS individuals had more LV concentric remodeling. MHD-POS participants had worse diastolic

function, with increased A waves, lower E/A ratios, and increased left atrial size indexes.

Biomarkers

Relationship to clinical characteristics

Whereas NT-proBNP and FSTL3 were not different among the 3 groups, GAL3 was higher in MHD-POS participants than in controls or MHD-NEG individuals (Table 1). Among all MHD participants, GAL3 correlated with age ($\rho=0.34$, $P<0.001$), eGFR ($\rho=-0.32$, $P<0.001$), and diabetes mellitus ($\rho=0.23$, $P=0.007$) but not with height, weight, BMI, or hypertension (all $P>0.05$). FSTL3 correlated with age ($\rho=0.35$, $P<0.001$), weight ($\rho=0.27$, $P=0.002$), BMI ($\rho=0.17$, $P=0.05$),

Table 2. Cardiac Structure and Function

	Nonobese Controls (n=21)	Obese MHD-NEG (n=52)	Obese MHD-POS (n=94)	P Value
Left heart parameters				
LV diastolic dimension, mm	45±4	46±4	46±5	0.54
LVEDV, mL	72 (61–80)	79 (68–93)	86 (71–104)*	0.01
LVEDV index, mL/m ²	40±9	40±10	41±10	0.61
LVM, g	112±24	142±31*	173±48*†	<0.001
LVM index, g/m ^{2.7}	28±6	36±6*	44±12*†	<0.001
LVM/LVEDV, g/mL	1.6±0.3	1.8±0.4	2.0±0.5*†	<0.001
Relative wall thickness	0.4±0.1	0.4±0.1	0.5±0.1*†	<0.001
LVEF, %	64±6	65±6	64±7	0.56
Mitral E wave, cm/s	70±13	83±17	78±19	0.03
Mitral A wave, cm/s	53±15	58±14	71±13*†	<0.001
Mitral E/A ratio	1.4±0.4	1.5±0.4	1.1±0.3*†	<0.001
Mean e' wave, cm/s	12±2	11±2	9±2*†	<0.001
E/e' ratio	6±1	8±2	9±3*†	<0.001
Left atrial diameter, mm	31±4	36±5*	38±5*	<0.001
LAV index (BSA), mL/m ²	32±11	29±8	34±9*	0.003
LAV index (height), mL/height ^{2.7}	14±5	15±4	19±5*†	<0.001
Right heart parameters				
RV basal diameter, mm	36±5	36±5	39±5	0.01
TAPSE, mm	23±4	23±3	23±4	0.97
Right atrial area, cm ²	14±3	14±3	17±4†	<0.001
PAAT, ms	181±29	168±14	106±19*†	<0.001
PASP, mm Hg	25±6	27±4	48±9*†	<0.001
TAPSE/PASP (mm/mm Hg)	1.0 (0.7–1.2)	0.8 (0.8–1.0)*	0.5 (0.4–0.6)*†	<0.001

Data are mean±SD, median (interquartile range), or n (%). P values reflect overall group differences with ANOVA comparison across all 3 groups; symbol denotes between-group comparisons with Bonferroni adjustment. BSA indicates body surface area; LAV, Left atrial volume; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; PAAT, pulmonary artery acceleration time; PASP, pulmonary artery systolic pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

* $P<0.02$ vs controls.

† $P<0.02$ vs obese MHD-NEG participants.

hypertension ($\rho=0.29$, $P<0.001$), diabetes mellitus ($\rho=0.25$, $P=0.004$), and eGFR ($\rho=-0.24$, $P=0.006$). In contrast, NT-proBNP did not correlate with any clinical characteristic in the MHD-POS or MHD-NEG participants, including hypertension, diabetes mellitus, eGFR, and BMI.

Relationship to cardiac structure and function

Among the MHD participants, both GAL3 and FSTL3 correlated with measures of LV diastolic function (mean e' velocity, E/A ratio, and E/e' ratio), PASP, and the TAPSE/PASP ratio but did not correlate with LV volume or mass (Table 3 and Figure 2). By comparison, NT-proBNP did not correlate with mean e' velocity, E/e' ratio, or LV mass or volume and correlated only with E/A.

Cardiac Structure and Function and Pulmonary Hemodynamics in MHD

LVH and diastolic function

Of the MHD-POS participants, 7% had isolated LVH, 59% had isolated abnormal diastolic function, and 34% had both LVH and diastolic dysfunction. Among these MHD-POS participants, BMI was strongly correlated to LV mass indexed to height^{2.7} ($\rho=0.52$, $P<0.001$) but not with mean e' ($\rho=0.17$, $P=0.10$). Among the MHD-POS participants, 38% had concentric remodeling, 30% had concentric hypertrophy, and 12% had eccentric hypertrophy.

Pulmonary hypertension

Among all obese participants (both MHD-POS and MHD-NEG), PASP correlated with several measures of abnormal diastolic function including increased left atrial volume index ($\rho=0.24$, $P=0.004$), decreased mitral E/A ratio ($\rho=-0.37$, $P<0.001$), increased E/e' ($\rho=0.33$, $P<0.001$), and decreased mean e' ($\rho=-0.46$, $P<0.001$; Figure 3A). In addition, PASP correlated with increases in LV mass/volume ratio ($\rho=0.27$, $P=0.001$) and LV mass indexed to height^{2.7} ($\rho=0.35$, $P<0.001$; Figure 3B). In multivariate linear regression models with clinical variables, age ($P=0.01$), waist circumference ($P=0.01$), and diabetes mellitus (0.03) all associated with PASP. Mean e' ($P=0.002$), E/A ratio ($P=0.02$), left atrial volume index ($P=0.002$), and LV mass indexed to height^{2.7} ($P=0.009$) were all independently predictive of PASP in echocardiographic multivariate models.

RV uncoupling

Although TAPSE was similar across the 3 groups (Table 2), elevation of PASP in the MHD-POS group was associated with a decrease in the TAPSE/PASP ratio suggestive of early right ventricle–pulmonary artery uncoupling (Figure 4A). Mean e' was correlated with TAPSE/PASP ($\rho=0.51$, $P<0.001$; Figure 4B) and remained significant after adjustment for age,

Table 3. Echocardiographic Correlates With Biomarkers in Obese Participants

Biomarker	Variable	ρ	P Value
GAL3	Diastolic function		
	Mean e'	-0.30	<0.001
	Mitral E/A ratio	-0.27	0.002
	E/e'	0.30	<0.001
	LAV indexed to BSA	-0.04	0.68
	LV remodeling		
	LVM indexed to height ^{2.7}	-0.05	0.56
	LVM/LVEDV ratio, g/mL	0.07	0.47
	Right heart structure/function		
	TAPSE	0.01	0.91
	PASP	0.33	<0.001
	TAPSE/PASP ratio	-0.30	0.002
	FSTL3	Diastolic function	
Mean e'		-0.35	<0.001
Mitral E/A ratio		-0.34	<0.001
E/e'		0.31	<0.001
LAV indexed to BSA		-0.21	0.02
LV remodeling			
LVM indexed to height ^{2.7}		0.04	0.67
LVM/LVEDV ratio, g/mL		0.12	0.19
Right heart structure/function			
TAPSE		-0.03	0.80
PASP		0.21	0.02
TAPSE/PASP ratio		-0.24	0.02
NT-proBNP		Diastolic function	
	Mean e'	-0.08	0.40
	Mitral E/A ratio	-0.20	0.03
	E/e'	0.08	0.42
	LAV indexed to BSA	-0.05	0.59
	LV remodeling		
	LVM indexed to height ^{2.7}	0.05	0.59
	LVM/LVEDV ratio, g/mL	-0.03	0.78
	Right heart structure/function		
	TAPSE	0.04	0.67
	PASP	0.11	0.25
	TAPSE/PASP ratio	-0.18	0.08

BSA indicates body surface area; FSTL3 indicates follistatin-like 3 peptide; GAL3, galectin-3; LAV, left atrial volume; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVM, left ventricular mass; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

sex, LV ejection fraction, and LV mass indexed to height^{2.7} ($P=0.001$), suggesting a relationship between RV uncoupling and diastolic dysfunction.

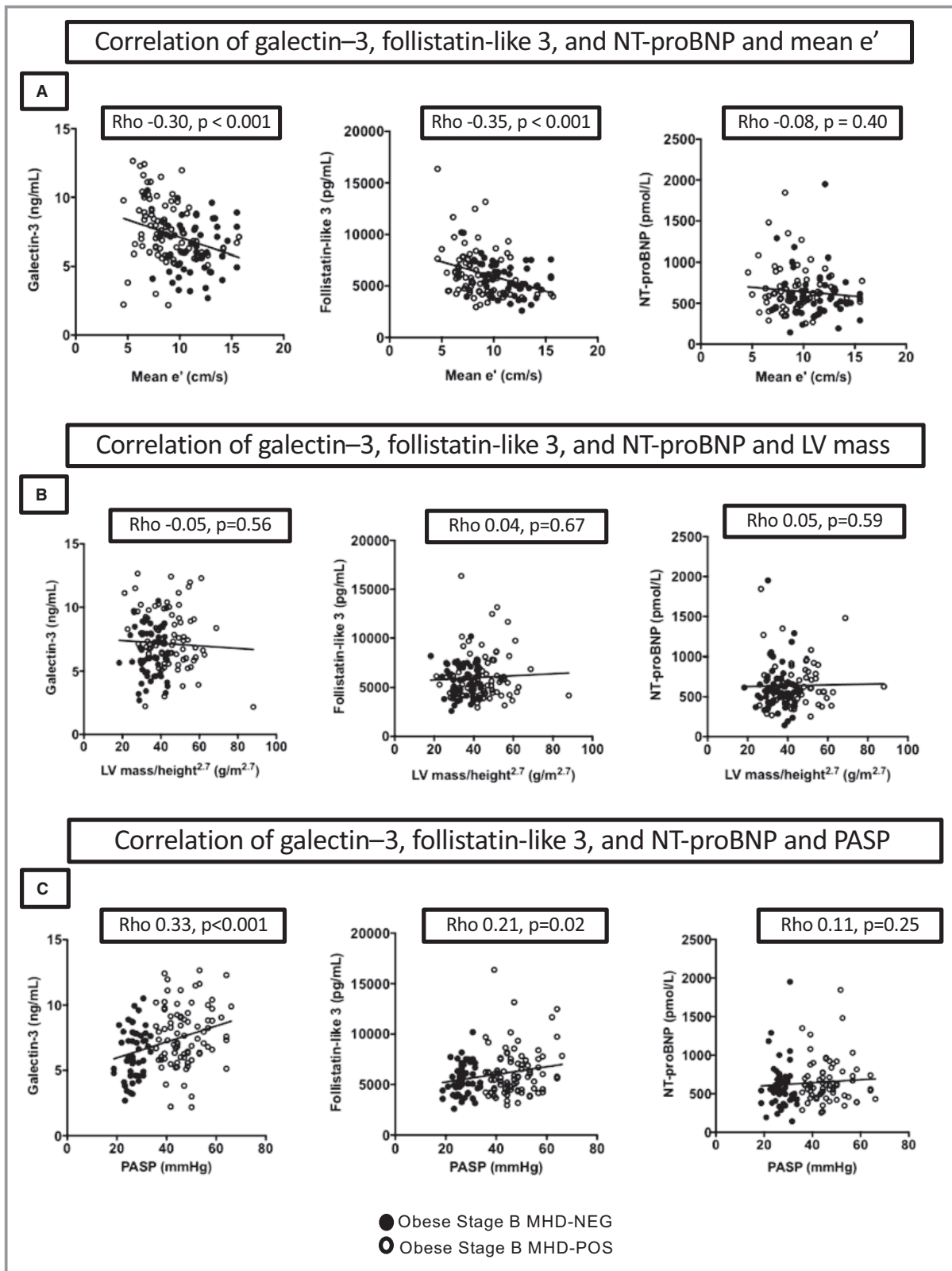


Figure 2. Correlations of biomarkers GAL3 (galectin-3), FSTL3 (follistatin-like 3 peptide), and NT-proBNP (N-terminal pro-B-type natriuretic peptide) with diastolic function, LV mass, and pulmonary pressures. **A**, Biomarker correlations with mean e' velocity. **B**, Biomarker correlations with LV mass indexed to height.^{2,7} **C**, Biomarker correlations with PASP. LV indicates left ventricular; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; PASP, pulmonary artery systolic pressure.

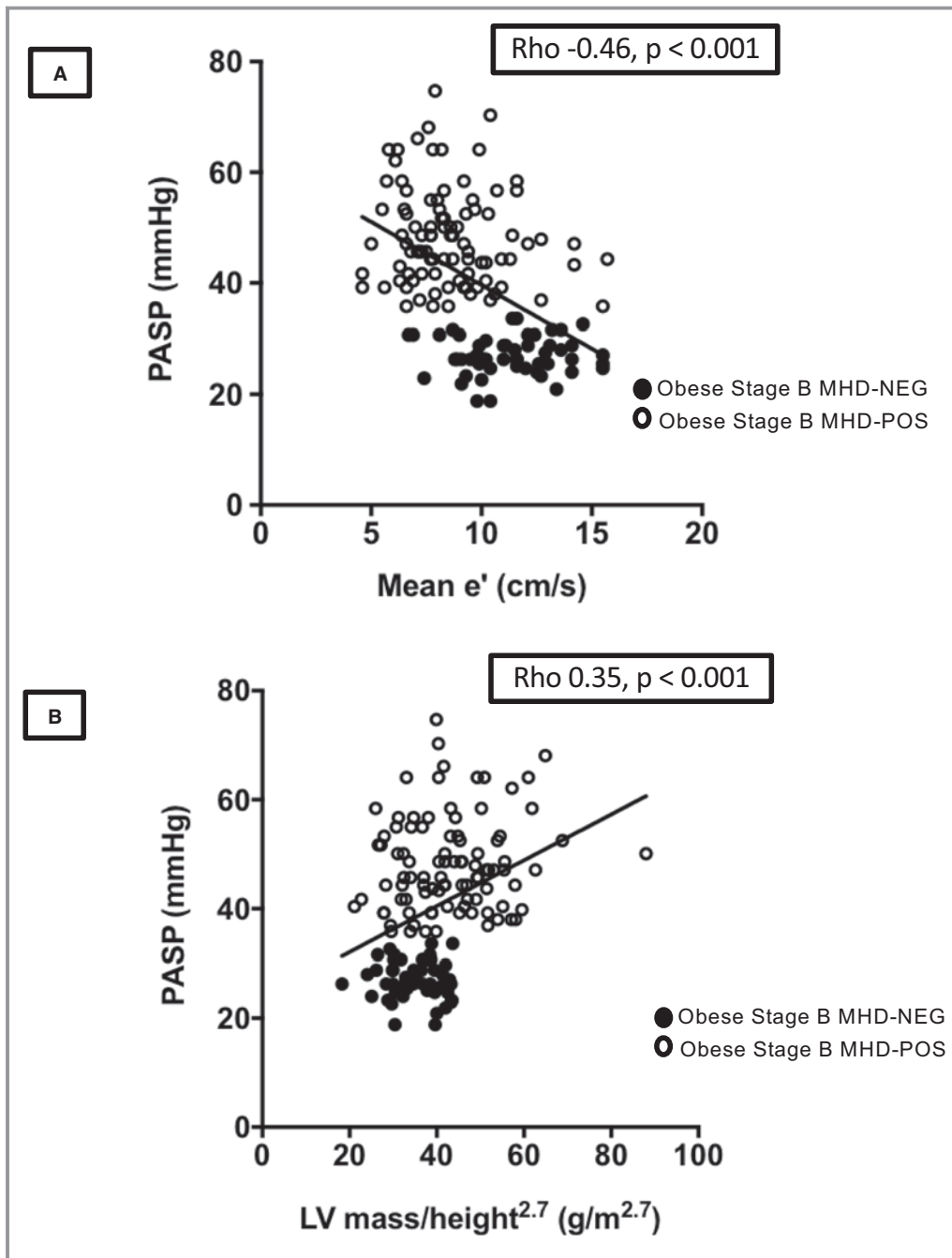


Figure 3. Relationship of left-sided cardiac disease and pulmonary pressures in obese participants. **A**, Correlation of mean e' velocity and PASP. **B**, Correlation of LV mass indexed to height^{2.7} and PASP. LV indicates left ventricular; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; PASP, pulmonary artery systolic pressure.

Primary Analysis: Clinical and Biomarker Correlates of MHD

Significant univariate clinical correlates of MHD-POS individuals included age, female sex, hypertension, diabetes mellitus, waist circumference, and hyperlipidemia (Table S2). Among

the 3 candidate biomarkers, GAL3 was associated with MHD-POS individuals in univariate analysis, whereas FSTL3 and NT-proBNP were not. In age- and sex-adjusted multivariate logistic regression models (Table 4), GAL3 was the only biomarker that remained associated with MHD-POS participants (odds ratio: 1.30; 95% CI, 1.01–1.68; $P=0.04$).

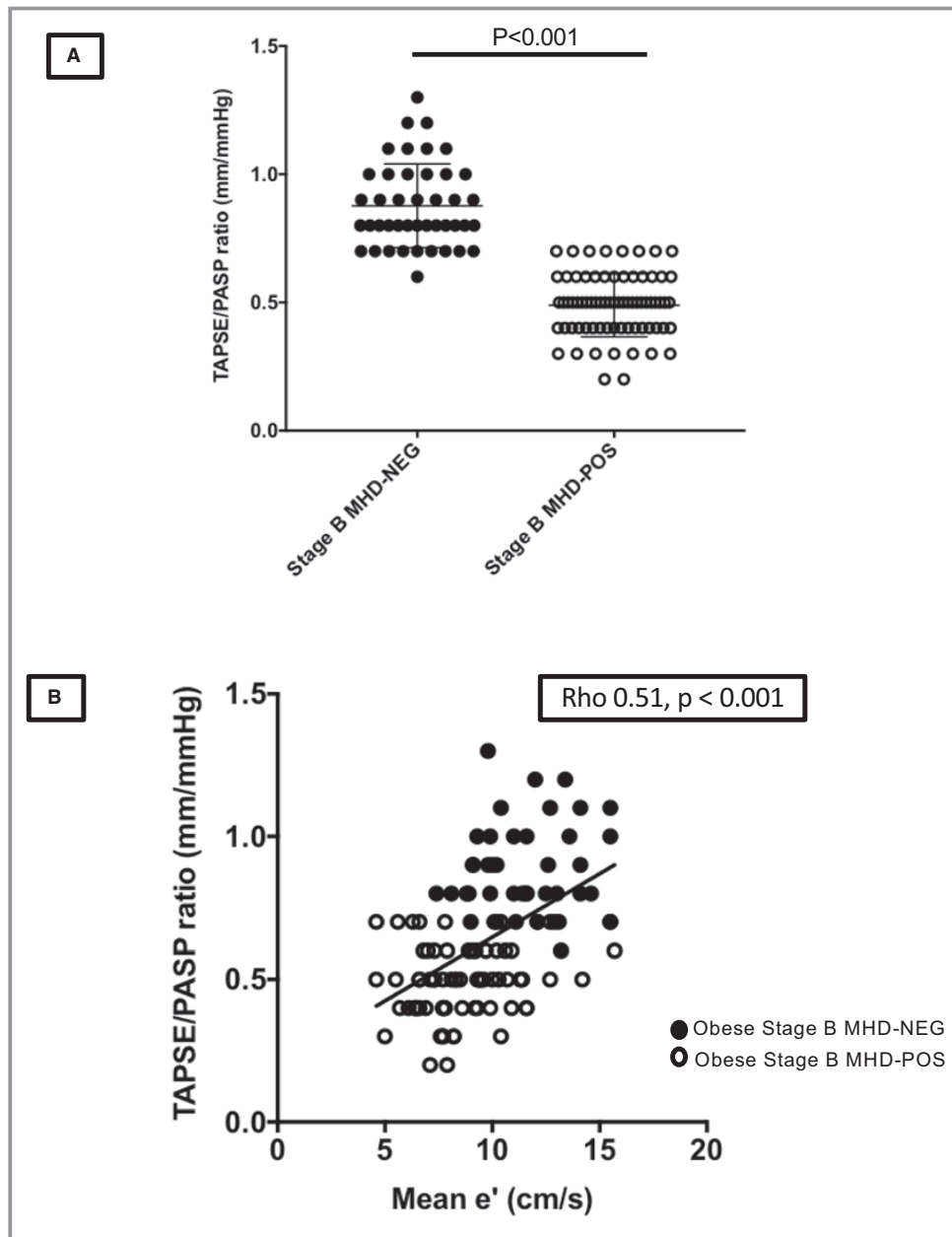


Figure 4. RV mechanics in stage B metabolic heart disease. **A**, Uncoupling of RV and pulmonary circulation in stage B metabolic heart disease. **B**, Relationship of LV diastolic function on RV mechanics in obese participants. LV indicates left ventricular; MHD, metabolic heart disease; MHD-NEG, metabolic heart disease–negative; MHD-POS, metabolic heart disease–positive; PASP, pulmonary artery systolic pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion.

Secondary Analysis: Clinical and Biomarker Predictors of PH Presence

In a secondary analysis, obese participants were classified as PH-POS solely on the basis of PASP ≥ 35 mm Hg or PH-NEG if PASP was < 35 mm Hg (Figure 1B). This criterion identified 138 obese PH-POS participants and 94 PH-NEG participants (Tables S3 and S4). In the PH-POS individuals, (1) PASP correlated with mean e' ($\rho = -0.30$, $P < 0.001$; Figure S1A), (2)

PASP correlated with LV mass indexed to height^{2.7} ($\rho = -0.17$, $P = 0.01$), and (3) mean e' correlated with the TAPSE/PASP ratio ($\rho = 0.33$, $P < 0.001$; Figure S1B). Similar univariate predictors of MHD PH-POS individuals were noted, as seen in the former analysis (Table S5). As in the primary analysis, multivariate models with age and sex adjustment showed that only GAL3 was associated with PH-POS participants (odds ratio: 1.33; 95% CI, 1.11–1.59; $P = 0.002$; Table S6).

Table 4. Logistic Regression Analysis for Presence of Obese Stage B MHD Phenotype

	OR (95% CI)	P Value
GAL3		
Model 1: Age and sex	1.28 (1.03–1.59)	0.004
Model 2: Clinical risk model	1.24 (1.01–1.53)	0.05
Model 3: Model 1+FSTL3* +NT-proBNP*	1.30 (1.01–1.68)	0.04
FSTL3*		
Model 1: Age and sex	0.71 (0.57–1.36)	0.56
Model 2: Clinical risk model	0.84 (0.53–1.35)	0.47
Model 3: Model 1+GAL3+ NT-proBNP*	0.67 (0.41–1.10)	0.11
NT-proBNP*		
Model 1: Age and sex	1.39 (0.85–2.28)	0.19
Model 2: Clinical risk model	1.32 (0.83–2.11)	0.24
Model 3: Model 1+GAL3+FSTL3*	1.49 (0.89–2.49)	0.13

Clinical risk model: history of hypertension, diabetes mellitus, hyperlipidemia, waist circumference, and estimated glomerular filtration rate in addition to biomarker of interest. FSTL3 indicates follistatin-like 3 peptide; GAL3, galectin-3; MHD, metabolic heart disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio. *FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker.

Discussion

The goal of this study was to determine whether biomarkers can be used for the early identification of preclinical (ie, ACC/AHA stage B) HF in a cohort of asymptomatic young obese participants. For the purpose of this analysis, stage B MHD was defined by the presence of increased LV mass and/or diastolic dysfunction that was accompanied by PH. There were 2 major findings. First, of the 3 biomarkers tested, we found that only GAL3 independently identified stage B MHD in otherwise asymptomatic young obese participants. Second, we found that in young obese participants, resting PH (1) is common, occurring in 59% participants; (2) correlates strongly with LV diastolic dysfunction and LVH; (3) correlates with RV uncoupling (lower TAPSE/PASP ratio); and (4) correlates with GAL3.

Classification of Stage B MHD Using LVH, Diastolic Dysfunction, and PH

Obesity is associated with an increased risk of incident HF,^{3,4} and mounting evidence suggests that among patients with HFpEF, there is a distinct “metabolic” phenotype with obesity, type 2 diabetes mellitus, and/or metabolic syndrome.²⁸ Obesity has been linked with subclinical alterations in cardiac structure (LVH) and function (diastolic dysfunction), which are

generally viewed as cardiac hallmarks of MHD.^{29,30} These structural and functional alterations are common in patients with obesity and may remain asymptomatic for extended periods. Importantly, LVH and diastolic dysfunction are important drivers in the progression to clinical HF, particularly HFpEF.³¹ A recent meta-analysis that polled 7564 participants from 5 studies showed that asymptomatic diastolic dysfunction contributed to a 70% higher risk of progressing to clinical HF compared with participants without diastolic dysfunction.³²

For this study, we defined MHD as the presence of diastolic dysfunction and/or LVH in the presence of PH. Diastolic dysfunction alone was prevalent in 59% of the MHD-POS individuals in our study. As expected, in these participants, the A wave was increased, the E/A ratio was decreased, and the left atrium was larger. LVH was present in 7% of MHD-POS participants; both entities, diastolic dysfunction and LVH, were present in 34%. The prevalence of LVH in our study (41%) is consistent with many prior observations, including a recent meta-analysis of 22 studies in which the average prevalence of LVH in obese participants was 56% (range: 20–85%).¹ As expected, LVH correlated with diastolic dysfunction, but as we³³ and others³⁴ have noted, there are many patients in whom diastolic dysfunction is not associated with LVH.

A novel key aspect of this study is the inclusion of PH, in addition to LVH and/or diastolic dysfunction, in the identification of patients with MHD. The functionally important consequence of impaired LV relaxation and/or filling is an elevation in pulmonary artery pressures, which plays a pathophysiologic role in HFpEF patients.¹⁷ PH is a major determinant of clinical symptoms and outcomes in patients with symptomatic HFpEF.³⁵ An inherent limitation of using diastolic relaxation and/or LVH to define MHD is that both measures are only indirectly related to PH. PASP was determined using PAAT, an approach that allowed pulmonary artery pressure to be estimated in >90% of patients in this study. Participants were deemed to have MHD only if diastolic dysfunction and/or LVH were associated with PH, which was defined as a resting PASP ≥ 35 mm Hg. Of the 250 obese participants in this study with analyzable echocardiographic data, 59% had LVH or diastolic dysfunction. With the additional requirement for PH, the number of obese participants classified as MHD-POS decreased to 94 patients (38% of obese individuals included in the primary analysis). PASP correlated significantly with mean e' ($\rho = -0.46$) and LV mass ($\rho = 0.35$), indicating that LV disease was a major determinant of the elevated pulmonary pressures noted in the obese cohort. The goal of this added criterion was to increase the specificity of the definition of MHD. As discussed later, the use of PH alone as the definition of MHD for a secondary analysis was also robust, likely reflecting the ability of PH to provide an integrated measure of the hemodynamic severity of left-sided dysfunction.

NT-proBNP Fails to Associate With MHD

Natriuretic peptides are well-established biomarkers for prognosis in HF patients.¹⁰ However, on the order of 30% of patients with established HFpEF—most notably, those who are younger and/or obese—have normal BNP levels,³⁶ likely related to the observation that obesity and metabolic disease are associated with lower circulating natriuretic peptides.³⁷ Conversely, natriuretic peptides are useful screening biomarkers for the detection of patients at risk for HF. In STOP-HF (Natriuretic Peptide-Based Screening and Collaborative Care for HF) and PONTIAC (NT-proBNP Selected Prevention of Cardiac Events in a Population of Diabetic Patients Without a History of Cardiac Disease), natriuretic levels were used to randomize stage A patients to intensive therapy, which led to decreased rates of incident HF and hospitalization. Although the recruitment of these cohorts did not specifically target obesity or metabolic syndrome, the average BMIs suggested that enrollees, on average, were overweight (STOP-HF) or had class 1 obesity (PONTIAC).^{38,39} Therefore, it seemed possible that NT-proBNP could be useful for the identification of stage B HF in our young obese population.

In our cohort, however, NT-proBNP proved to be an ineffective biomarker for detection of stage B HF due to MHD. There were no differences in NT-proBNP levels between MHD-POS and MHD-NEG individuals and no significant associations with clinical characteristics (eg, hypertension, diabetes mellitus, eGFR, and BMI) or measures of cardiac structure (ie, LVH, LV volume, RV parameters), most measures of diastolic function (mean e' , LA size, E/e' ratio), or PH. The failure of NT-proBNP to identify stage B MHD likely relates to confounding factors that suppress circulating natriuretic levels in the setting of obesity.³⁷

FSTL3 Correlates to Metabolic Disease But Not MHD

FSTL3, like natriuretic peptides, is a cardiac myokine. FSTL3 appears to play a role in the regulation of myocyte growth and mediates paracrine activation of fibroblasts in the heart.⁴⁰ *FSTL3* gene expression increases in myocardium from patients with severe HF undergoing therapy with an LV assist device.¹⁵ FSTL3 also has a role in metabolic regulation; levels are increased in obesity,⁴¹ and deletion in mice leads to favorable visceral fat and glucose homeostasis.⁴² Because the levels of FSTL3 are increased in HF and there is no apparent suppression of levels in obesity, we reasoned that FSTL3 might be a useful biomarker for stage B MHD in obese individuals. Interestingly, in our population, plasma FSTL3 levels were higher in obese participants, particularly in those with MHD, and correlated significantly with diastolic indexes (mean e' , E/A ratio, E/e'

ratio) and higher PASP but not with LVH. However, in univariate and fully adjusted multivariate models, FSTL3 was not able to identify MHD among obese patients, suggesting that in these patients FSTL3 may reflect the abnormal metabolic milieu rather than the cardiac phenotype.

GAL3 Is Associated With MHD

A major finding of this study is that GAL3 is associated with stage B HF due to MHD in young obese individuals, and in particular, GAL3 links strongly to diastolic dysfunction and PH. In contrast to FSTL3, this association persisted with multivariable adjustments including age, sex, and clinical risk factors (hypertension, diabetes mellitus, hyperlipidemia, waist circumference, and eGFR). Prior studies have shown that plasma GAL3 levels are increased in both HFpEF patients and those with HF with reduced ejection fraction.⁴³ In stage C HFpEF individuals, GAL3 is associated with poor outcomes.⁴⁴ Likewise, GAL3 predicted incident HF in multivariate models in the Framingham Heart Study.⁴⁵ Ours is the first study to test the role of GAL3 in predicting a preclinical HF phenotype in asymptomatic young obese individuals at high risk of HF development.

The mechanism responsible for elevated GAL3 in our participants likely relates to the underlying myocardial process. GAL3, a β -galactoside binding lectin derived from macrophages, promotes cardiac fibroblast proliferation, collagen production, and inflammation and is associated with LV dysfunction.⁴⁶ In mice, the inhibition of GAL3 blocked myocardial fibrosis, inflammation, and superoxide levels cause by a high-fat diet, suggesting that GAL3 may play pathophysiologic role in cardiac dysfunction with obesity.⁴⁷ Because LV diastolic dysfunction is a primary process in MHD, it is likely that GAL3 in some way reflects the biology of that process.

GAL3 Associates With PH

The measurement of PASP using PAAT allowed for several important findings. First, it provided the novel demonstration that GAL3 strongly associates with PH in these asymptomatic participants. PH was surprisingly common, occurring in 59% of the young asymptomatic obese participants in our study. Although prior studies have not assessed PH in asymptomatic young obese individuals, our findings are consistent with those of Brittain et al, who found that PH was associated with insulin resistance and diastolic dysfunction in a middle-aged population.⁴⁸ The implications of PH in our population are not clear; however, PH is a powerful predictor of mortality in patients with symptomatic HF³⁵ and predicts HF admissions among black patients.³ It is also noteworthy that among our participants, PH was associated with early evidence of RV uncoupling, which portends a worse prognosis in patients with HFpEF.⁴⁹

The source of the elevated GAL3 in our participants cannot be completely determined from this study. PH correlated with left heart disease in these individuals—in particular, diastolic dysfunction and LVH—suggesting that PH may be secondary to elevated left heart filling pressures. PH due to left heart disease (World Health Organization group 2) is the most frequent cause of PH worldwide. In addition, it is noteworthy that in patients with pulmonary arterial hypertension, GAL3 is associated with RV dysfunction,⁵⁰ raising the possibility that among our participants, elevated GAL3 may in part reflect release from the lungs and/or the right ventricle in addition to the left heart.

Limitations

Because this study was noninvasive, we did not have invasive hemodynamics to exclude patients who may have had elevated pulmonary pressures not related to left-sided disease (occult pulmonary embolism, significant obstructive sleep apnea, primary PH). However, with the mandatory inclusion of left-sided cardiac disease, as reflected by LVH and/or diastolic dysfunction, we attempted to identify individuals who likely had PH due to left-sided disease; individuals with any known pulmonary disease were excluded from the study. The sample size was diminished given exclusion of patients whose MHD status was indeterminate. However, the secondary analysis, which was based on the presence or absence of PH and included all 232 evaluable patients, confirmed the association of GAL3 with MHD.

Conclusions

We showed that stage B MHD and PH are common in asymptomatic young individuals who are obese. GAL3 is independently associated with MHD and PH in these high-risk individuals, even among traditional risk factors, whereas NT-proBNP and FSTL3 are not. The strong relationship between PH and GAL3 raises the possibility that GAL3 is involved in the pathophysiology of PH in metabolic disease and/or that PH itself may lead to an increase in GAL3 levels. GAL3 may be of value in identifying preclinical HF and/or PH in obese individuals, a targetable group for preventative HF interventions.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of persons removed from Stage B MHD primary analysis due to indeterminate status.

	Obese indeterminate (n=85)	All obese patients in primary analysis (n=146)	P value
Age, y	40 ± 11	43 ± 11	0.09
Female, n (%)	60 (71)	116 (79)	0.31
Black, n (%)	48 (56)	95 (65)	0.37
Body mass index, kg/m ²	41 ± 11	39 ± 8	0.09
Diabetes	31 (36)	43 (29)	0.27
Hypertension	44 (52)	76 (52)	0.97
Current smoking	13 (15)	17 (11)	0.43
Obstructive sleep apnea	17 (20)	26 (18)	0.70
Hyperlipidemia	34 (40)	64 (44)	0.57
Metabolic syndrome	70 (82)	107 (73)	0.12
HDL, mg/dL	43 ± 10	46 ± 11	0.03
Triglycerides, mg/dL	134 (81-186)	111 (77-173)	0.34
eGFR, mL/min/1.73m ²	135 ± 34	124 ± 27	0.02
NT-proBNP, pmol/L	562 (415-701)	574 (458-729)	0.69
GAL3, ng/mL	7 ± 2	7 ± 2	0.21
FSTL3, pg/mL	5417 (4514-6471)	5721 (4477-7101)	0.26
LVM index, g/ht ^{2.7}	43 ± 11	41 ± 11	0.30
LVM/LVEDV, g/mL	1.8 (1.6-2.2)	1.9 (1.6-2.2)	0.82
LVEF, %	63 ± 7	65 ± 6	0.24
Mitral E/A ratio	1.3 ± 0.3	1.2 ± 0.4	0.12
Mean e' wave, cm/s	10 ± 2	10 ± 3	0.09
E/e' ratio	8 ± 2	9 ± 3	0.05
Left atrial volume index (BSA), mL/m ²	32 ± 10	33 ± 9	0.81
RV basal diameter, mm	38 ± 5	38 ± 5	0.34
TAPSE, mm	24 ± 4	23 ± 3	0.31
PA acceleration time, ms	132 ± 34	128 ± 35	0.28
PA systolic pressure, mmHg	39 ± 12	41 ± 13	0.28
TAPSE/PA systolic pressure (mm/mmHg)	0.61 (0.47-0.77)	0.58 (0.45-0.77)	0.34

Data are mean ± SD, median (interquartile range), or n (%). P value between group comparisons. MHD = metabolic heart disease; LV, left ventricle; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery

Table S2. Logistic regression analysis of predictors of obese MHD phenotype.

	OR (95% CI)	P value
Age	1.11 (1.07-1.15)	<0.001
Female sex	0.29 (0.11-0.82)	0.02
Black	1.09 (0.68-1.75)	0.73
Hypertension	3.97 (1.93-8.19)	<0.001
Diabetes	4.98 (1.93-12.81)	<0.001
BMI	1.05 (1.00-1.10)	0.06
Waist circumference	1.03 (1.00-1.05)	0.03
Hyperlipidemia	3.08 (1.48-6.43)	0.003
eGFR	0.99 (0.98-1.00)	0.19
GAL3	1.35 (1.13-1.62)	0.001
FSTL3*	1.30 (0.91-1.85)	0.15
NT-proBNP*	1.36 (0.88-2.09)	0.17

BMI, body mass index; eGFR, estimated glomerular filtration rate; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

Table S3. Baseline characteristics of cohort with MHD PH phenotype.

	Non-obese controls (n=21)	Obese MHD PH-NEG (n=94)	Obese MHD PH-POS (n=138)	P value
Age, y	43 ± 12	40 ± 11	43 ± 11	0.05
Female, n (%)	18 (86)	99 (84)	99 (72)	0.10
Black, n (%)	9 (43)	58 (62)	86 (62)	0.03
Anthropometrics				
Height, m	167 ± 6	166 ± 11	167 ± 9	0.54
Ideal body weight, kg	60 ± 6	58 ± 11	60 ± 9	0.41
Actual body weight, kg	72 (64-74)	105 (87-119)*	114 (96-127)*	<0.001
Body mass index, kg/m ²	25 (22-26)	36 (32-43)*	39 (34-45)*	<0.001
Body surface area, m ²	1.8 ± 0.1	2.1 ± 0.3*	2.2 ± 0.3*	<0.001
Waist circumference, cm	81 (74-91)	117 (102-122)	121 (107-132)*†	<0.001
Comorbidities, n (%)				
Diabetes	0 (0)	18 (19)	56 (41)	<0.001
Hypertension	0 (0)	39 (41)	82 (59)	<0.001
Current smoking	1 (4)	10 (11)	20 (14)	0.02
Obstructive sleep apnea	0 (0)	16 (17)	27 (20)	0.04
Hyperlipidemia	1 (5)	29 (31)	69 (50)	<0.001
Metabolic syndrome	0 (0)	58 (62)	120 (87)	<0.001
Medications, n (%)				
ACEI or ARB	0 (0)	21 (22)	59 (43)	<0.001
β-Blocker	0 (0)	17 (18)	28 (20)	0.03
Oral hypoglycemic agent	0 (0)	15 (16)	40 (29)	<0.001
Insulin	0 (0)	5 (5)	18 (13)	0.04
Laboratory values				
Total cholesterol, mg/dL	184 (178-217)	180 (154-207)	186 (163-203)	0.36
HDL, mg/dL	61 (52-67)	44 (38-50)*	43 (38-50)*	<0.001
Triglycerides, mg/dL	60 (48-84)	104 (74-174)	126 (82-185)*	0.003
Triglyceride/HDL ratio	1.1 (0.7-1.6)	2.5 (1.5-3.9)*	2.9 (1.9-4.3)*	0.002
eGFR, mL/min/1.73m ²	99 (16)	125 ± 27*	131 ± 33*	<0.001
Biomarkers				
NT-proBNP, pmol/L	420 (279-736)	554 (415-694)	589 (373-773)	0.58
GAL3, ng/mL	5.7 ± 1.6	6.4 ± 2.0	7.4 ± 2.2*†	<0.001
FSTL3, pg/mL	4665 (3976-5951)	5361 (4454-6772)	5594 (4492-7035)	0.65

Data are mean ± SD, median (interquartile range), or n (%). P value reflect overall group differences. MHD PH-NEG, metabolic heart disease pulmonary hypertension negative individuals; MHD PH-POS, metabolic heart disease pulmonary hypertension positive individuals; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide

*P<0.02 versus controls

†P<0.02 versus obese MHD PH-NEG individuals

Table S4. Cardiac structure and function with MHD PH phenotype.

	Non-obese controls (n=21)	Obese MHD PH-NEG (n=94)	Obese MHD PH-POS (n=138)	P value
<i>Left heart parameters</i>				
LV diastolic dimension, mm	45 ± 4	47 ± 5	46 ± 5	0.20
LV end-diastolic volume, mL	72 (61-80)	82 (71-104)	86 (73-105)*	0.02
LV end-diastolic volume index, mL/m ²	40 ± 9	42 ± 10	41 ± 9	0.77
LV mass, g	112 ± 24	165 ± 47*	166 ± 45*	<0.001
LVM index, g/ht ^{2.7}	28 ± 6	42 ± 11*	41 ± 11*	<0.001
LVM/LVEDV, g/mL	1.6 (1.37-1.83)	1.9 (1.6-2.2)*	1.9 (1.6-2.2)*	0.007
LVEF, %	64 ± 6	65 ± 7	63 ± 6	0.03
Mitral E wave, cm/s	70 ± 13	80 ± 17	79 ± 18	0.16
Mitral A wave, cm/s	53 ± 15	61 ± 14*	68 ± 13*	0.001
Mitral E/A ratio	1.4 ± 0.4	1.4 ± 0.4	1.2 ± 0.3*†	<0.001
Mean e' wave, cm/s	12 ± 2	11 ± 2	9 ± 2*†	<0.001
E/e' ratio	6 ± 1	8 ± 2*	9 ± 3*†	<0.001
Left atrial diameter, mm	31 ± 4	38 ± 5*	38 ± 4*	<0.001
Left atrial volume index (BSA), mL/m ²	32 ± 11	33 ± 10	32 ± 8	0.59
Left atrial volume index (ht), mL/ht ^{2.7}	14 ± 5	18 ± 7*	18 ± 5	0.08
<i>Right heart parameters</i>				
RV basal diameter, mm	36 ± 5	38 ± 5	38 ± 5	0.56
TAPSE, mm	23 ± 4	23 ± 4	23 ± 4	0.78
Right atrial area, cm ²	14 ± 3	15 ± 3	16 ± 3	0.06
PA acceleration time, ms	181 ± 29	164 ± 20	106 ± 18*†	<0.001
PA systolic pressure, mmHg	25 ± 6	28 ± 5	48 ± 8*†	<0.001
TAPSE/PA systolic pressure (mm/mmHg)	1.0 (0.7-1.2)	0.8 (0.7-1.0)*	0.5 (0.4-0.6) *†	<0.001

Data are mean ± SD, median (interquartile range), or n (%). P value reflect overall group differences. MHD PH-NEG, metabolic heart disease pulmonary hypertension negative individuals; MHD PH-POS, metabolic heart disease pulmonary hypertension positive individuals; LV, left ventricle; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; BSA, body surface area; ht, height; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery

*P<0.02 versus controls

†P<0.02 versus obese MHD PH-NEG individuals

Table S5. Logistic regression analysis of predictors of obese Stage B MHD PH phenotype.

	OR (95% CI)	P value
Age	1.03 (1.01-1.05)	0.02
Female sex	0.52 (0.27-1.00)	0.05
Black	0.99 (0.68-1.43)	0.94
Hypertension	2.07 (1.21-3.52)	0.008
Diabetes	2.89 (1.56-5.34)	<0.001
BMI	1.03 (1.00-1.06)	0.07
Waist circumference	1.02 (1.01-1.04)	0.003
Hyperlipidemia	2.24 (1.29-3.89)	0.004
eGFR	1.01 (1.00-1.02)	0.12
GAL3	1.26 (1.10-1.45)	0.001
FSTL3*	1.15 (0.87-1.52)	0.33
NT-proBNP*	1.33 (0.96-1.83)	0.09

BMI, body mass index; eGFR, estimated glomerular filtration rate; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

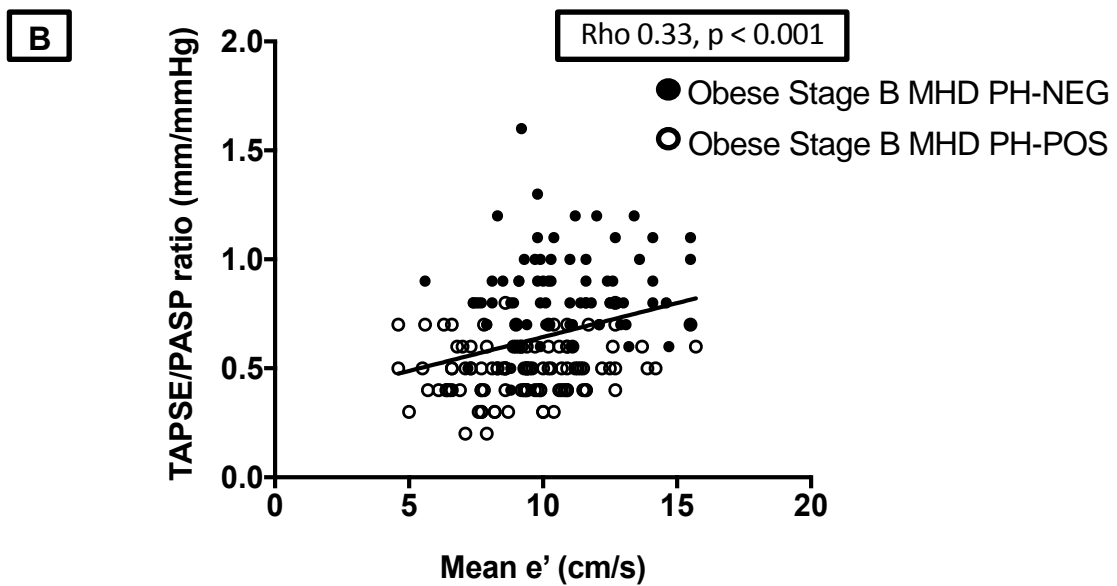
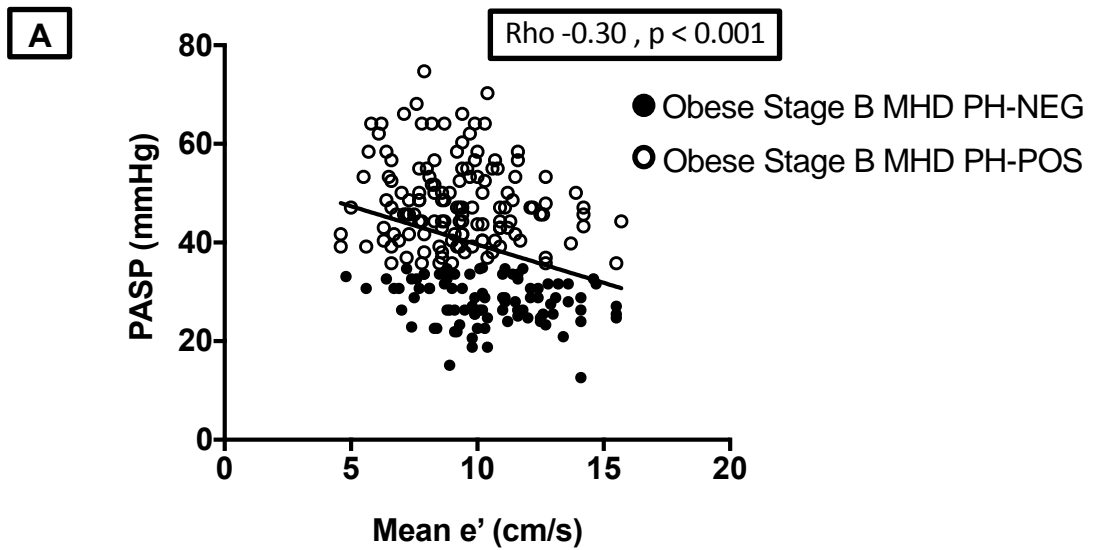
Table S6. Logistic regression analysis for presence of obese Stage B MHD PH phenotype.

	OR (95% CI)	P value
<i>GAL3</i>		
Model 1: Age and sex	1.26 (1.09-1.47)	0.003
Model 2: Clinical risk model	1.25 (1.06-1.46)	0.007
Model 3: Model 1 + FSTL3* + NT-proBNP*	1.33 (1.11-1.59)	0.002
<i>FSTL3*</i>		
Model 1: Age and sex	1.03 (0.76-1.39)	0.87
Model 2: Clinical risk model	0.92 (0.65-1.30)	0.63
Model 3: Model 1 + GAL3 + NT-proBNP*	0.85 (0.60-1.19)	0.33
<i>NT-proBNP*</i>		
Model 1: Age and sex	1.33 (0.96-1.84)	0.09
Model 2: Clinical risk model	1.31 (0.93-1.84)	0.12
Model 3: Model 1 + GAL3 + FSTL3*	1.37 (0.97-1.94)	0.08

GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide
 Clinical risk model: history of hypertension, diabetes, hyperlipidemia, waist circumference, and estimated glomerular filtration rate in addition to biomarker of interest

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

Figure S1. Correlations of diastolic function and right heart pressures and function in metabolic heart disease Stage B pulmonary phenotype.



A: Mean e' and PASP relationship; **B:** RV/pulmonary circulation metrics and mean e' relationship

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of persons removed from Stage B MHD primary analysis due to indeterminate status.

	Obese indeterminate (n=85)	All obese patients in primary analysis (n=146)	P value
Age, y	40 ± 11	43 ± 11	0.09
Female, n (%)	60 (71)	116 (79)	0.31
Black, n (%)	48 (56)	95 (65)	0.37
Body mass index, kg/m ²	41 ± 11	39 ± 8	0.09
Diabetes	31 (36)	43 (29)	0.27
Hypertension	44 (52)	76 (52)	0.97
Current smoking	13 (15)	17 (11)	0.43
Obstructive sleep apnea	17 (20)	26 (18)	0.70
Hyperlipidemia	34 (40)	64 (44)	0.57
Metabolic syndrome	70 (82)	107 (73)	0.12
HDL, mg/dL	43 ± 10	46 ± 11	0.03
Triglycerides, mg/dL	134 (81-186)	111 (77-173)	0.34
eGFR, mL/min/1.73m ²	135 ± 34	124 ± 27	0.02
NT-proBNP, pmol/L	562 (415-701)	574 (458-729)	0.69
GAL3, ng/mL	7 ± 2	7 ± 2	0.21
FSTL3, pg/mL	5417 (4514-6471)	5721 (4477-7101)	0.26
LVM index, g/ht ^{2.7}	43 ± 11	41 ± 11	0.30
LVM/LVEDV, g/mL	1.8 (1.6-2.2)	1.9 (1.6-2.2)	0.82
LVEF, %	63 ± 7	65 ± 6	0.24
Mitral E/A ratio	1.3 ± 0.3	1.2 ± 0.4	0.12
Mean e' wave, cm/s	10 ± 2	10 ± 3	0.09
E/e' ratio	8 ± 2	9 ± 3	0.05
Left atrial volume index (BSA), mL/m ²	32 ± 10	33 ± 9	0.81
RV basal diameter, mm	38 ± 5	38 ± 5	0.34
TAPSE, mm	24 ± 4	23 ± 3	0.31
PA acceleration time, ms	132 ± 34	128 ± 35	0.28
PA systolic pressure, mmHg	39 ± 12	41 ± 13	0.28
TAPSE/PA systolic pressure (mm/mmHg)	0.61 (0.47-0.77)	0.58 (0.45-0.77)	0.34

Data are mean ± SD, median (interquartile range), or n (%). P value between group comparisons. MHD = metabolic heart disease; LV, left ventricle; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery

Table S2. Logistic regression analysis of predictors of obese MHD phenotype.

	OR (95% CI)	P value
Age	1.11 (1.07-1.15)	<0.001
Female sex	0.29 (0.11-0.82)	0.02
Black	1.09 (0.68-1.75)	0.73
Hypertension	3.97 (1.93-8.19)	<0.001
Diabetes	4.98 (1.93-12.81)	<0.001
BMI	1.05 (1.00-1.10)	0.06
Waist circumference	1.03 (1.00-1.05)	0.03
Hyperlipidemia	3.08 (1.48-6.43)	0.003
eGFR	0.99 (0.98-1.00)	0.19
GAL3	1.35 (1.13-1.62)	0.001
FSTL3*	1.30 (0.91-1.85)	0.15
NT-proBNP*	1.36 (0.88-2.09)	0.17

BMI, body mass index; eGFR, estimated glomerular filtration rate; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

Table S3. Baseline characteristics of cohort with MHD PH phenotype.

	Non-obese controls (n=21)	Obese MHD PH-NEG (n=94)	Obese MHD PH-POS (n=138)	P value
Age, y	43 ± 12	40 ± 11	43 ± 11	0.05
Female, n (%)	18 (86)	99 (84)	99 (72)	0.10
Black, n (%)	9 (43)	58 (62)	86 (62)	0.03
Anthropometrics				
Height, m	167 ± 6	166 ± 11	167 ± 9	0.54
Ideal body weight, kg	60 ± 6	58 ± 11	60 ± 9	0.41
Actual body weight, kg	72 (64-74)	105 (87-119)*	114 (96-127)*	<0.001
Body mass index, kg/m ²	25 (22-26)	36 (32-43)*	39 (34-45)*	<0.001
Body surface area, m ²	1.8 ± 0.1	2.1 ± 0.3*	2.2 ± 0.3*	<0.001
Waist circumference, cm	81 (74-91)	117 (102-122)	121 (107=132)*†	<0.001
Comorbidities, n (%)				
Diabetes	0 (0)	18 (19)	56 (41)	<0.001
Hypertension	0 (0)	39 (41)	82 (59)	<0.001
Current smoking	1 (4)	10 (11)	20 (14)	0.02
Obstructive sleep apnea	0 (0)	16 (17)	27 (20)	0.04
Hyperlipidemia	1 (5)	29 (31)	69 (50)	<0.001
Metabolic syndrome	0 (0)	58 (62)	120 (87)	<0.001
Medications, n (%)				
ACEI or ARB	0 (0)	21 (22)	59 (43)	<0.001
β-Blocker	0 (0)	17 (18)	28 (20)	0.03
Oral hypoglycemic agent	0 (0)	15 (16)	40 (29)	<0.001
Insulin	0 (0)	5 (5)	18 (13)	0.04
Laboratory values				
Total cholesterol, mg/dL	184 (178-217)	180 (154-207)	186 (163-203)	0.36
HDL, mg/dL	61 (52-67)	44 (38-50)*	43 (38-50)*	<0.001
Triglycerides, mg/dL	60 (48-84)	104 (74-174)	126 (82-185)*	0.003
Triglyceride/HDL ratio	1.1 (0.7-1.6)	2.5 (1.5-3.9)*	2.9 (1.9-4.3)*	0.002
eGFR, mL/min/1.73m ²	99 (16)	125 ± 27*	131 ± 33*	<0.001
Biomarkers				
NT-proBNP, pmol/L	420 (279-736)	554 (415-694)	589 (373-773)	0.58
GAL3, ng/mL	5.7 ± 1.6	6.4 ± 2.0	7.4 ± 2.2*†	<0.001
FSTL3, pg/mL	4665 (3976-5951)	5361 (4454-6772)	5594 (4492-7035)	0.65

Data are mean ± SD, median (interquartile range), or n (%). P value reflect overall group differences. MHD PH-NEG, metabolic heart disease pulmonary hypertension negative individuals; MHD PH-POS, metabolic heart disease pulmonary hypertension positive individuals; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide

*P<0.02 versus controls

†P<0.02 versus obese MHD PH-NEG individuals

Table S4. Cardiac structure and function with MHD PH phenotype.

	Non-obese controls (n=21)	Obese MHD PH-NEG (n=94)	Obese MHD PH-POS (n=138)	P value
Left heart parameters				
LV diastolic dimension, mm	45 ± 4	47 ± 5	46 ± 5	0.20
LV end-diastolic volume, mL	72 (61-80)	82 (71-104)	86 (73-105)*	0.02
LV end-diastolic volume index, mL/m ²	40 ± 9	42 ± 10	41 ± 9	0.77
LV mass, g	112 ± 24	165 ± 47*	166 ± 45*	<0.001
LVM index, g/ht ^{2.7}	28 ± 6	42 ± 11*	41 ± 11*	<0.001
LVM/LVEDV, g/mL	1.6 (1.37-1.83)	1.9 (1.6-2.2)*	1.9 (1.6-2.2)*	0.007
LVEF, %	64 ± 6	65 ± 7	63 ± 6	0.03
Mitral E wave, cm/s	70 ± 13	80 ± 17	79 ± 18	0.16
Mitral A wave, cm/s	53 ± 15	61 ± 14*	68 ± 13*	0.001
Mitral E/A ratio	1.4 ± 0.4	1.4 ± 0.4	1.2 ± 0.3*†	<0.001
Mean e' wave, cm/s	12 ± 2	11 ± 2	9 ± 2*†	<0.001
E/e' ratio	6 ± 1	8 ± 2*	9 ± 3*†	<0.001
Left atrial diameter, mm	31 ± 4	38 ± 5*	38 ± 4*	<0.001
Left atrial volume index (BSA), mL/m ²	32 ± 11	33 ± 10	32 ± 8	0.59
Left atrial volume index (ht), mL/ht ^{2.7}	14 ± 5	18 ± 7*	18 ± 5	0.08
Right heart parameters				
RV basal diameter, mm	36 ± 5	38 ± 5	38 ± 5	0.56
TAPSE, mm	23 ± 4	23 ± 4	23 ± 4	0.78
Right atrial area, cm ²	14 ± 3	15 ± 3	16 ± 3	0.06
PA acceleration time, ms	181 ± 29	164 ± 20	106 ± 18*†	<0.001
PA systolic pressure, mmHg	25 ± 6	28 ± 5	48 ± 8*†	<0.001
TAPSE/PA systolic pressure (mm/mmHg)	1.0 (0.7-1.2)	0.8 (0.7-1.0)*	0.5 (0.4-0.6) *†	<0.001

Data are mean ± SD, median (interquartile range), or n (%). P value reflect overall group differences. MHD PH-NEG, metabolic heart disease pulmonary hypertension negative individuals; MHD PH-POS, metabolic heart disease pulmonary hypertension positive individuals; LV, left ventricle; LVM, left ventricular mass; LVEF, left ventricular ejection fraction; BSA, body surface area; ht, height; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery

*P<0.02 versus controls

†P<0.02 versus obese MHD PH-NEG individuals

Table S5. Logistic regression analysis of predictors of obese Stage B MHD PH phenotype.

	OR (95% CI)	P value
Age	1.03 (1.01-1.05)	0.02
Female sex	0.52 (0.27-1.00)	0.05
Black	0.99 (0.68-1.43)	0.94
Hypertension	2.07 (1.21-3.52)	0.008
Diabetes	2.89 (1.56-5.34)	<0.001
BMI	1.03 (1.00-1.06)	0.07
Waist circumference	1.02 (1.01-1.04)	0.003
Hyperlipidemia	2.24 (1.29-3.89)	0.004
eGFR	1.01 (1.00-1.02)	0.12
GAL3	1.26 (1.10-1.45)	0.001
FSTL3*	1.15 (0.87-1.52)	0.33
NT-proBNP*	1.33 (0.96-1.83)	0.09

BMI, body mass index; eGFR, estimated glomerular filtration rate; GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

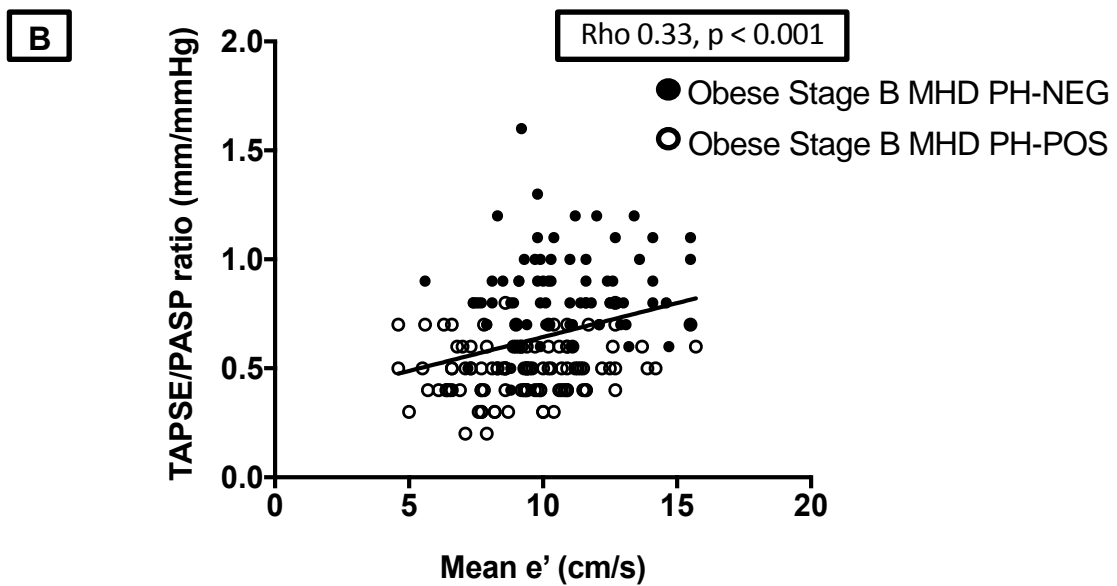
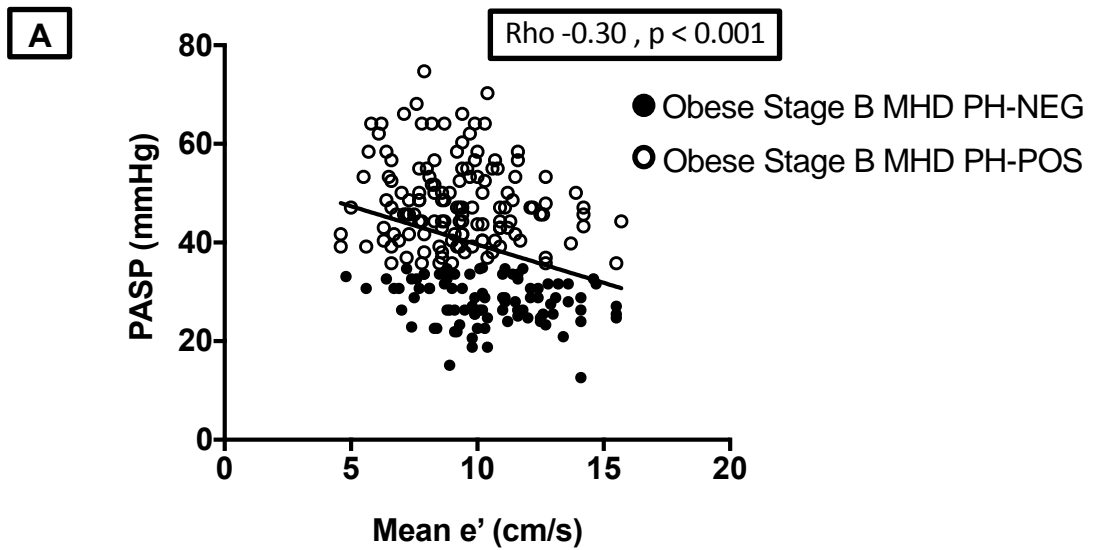
Table S6. Logistic regression analysis for presence of obese Stage B MHD PH phenotype.

	OR (95% CI)	P value
<i>GAL3</i>		
Model 1: Age and sex	1.26 (1.09-1.47)	0.003
Model 2: Clinical risk model	1.25 (1.06-1.46)	0.007
Model 3: Model 1 + FSTL3* + NT-proBNP*	1.33 (1.11-1.59)	0.002
<i>FSTL3*</i>		
Model 1: Age and sex	1.03 (0.76-1.39)	0.87
Model 2: Clinical risk model	0.92 (0.65-1.30)	0.63
Model 3: Model 1 + GAL3 + NT-proBNP*	0.85 (0.60-1.19)	0.33
<i>NT-proBNP*</i>		
Model 1: Age and sex	1.33 (0.96-1.84)	0.09
Model 2: Clinical risk model	1.31 (0.93-1.84)	0.12
Model 3: Model 1 + GAL3 + FSTL3*	1.37 (0.97-1.94)	0.08

GAL3, galectin-3; FSTL3, follistatin-like 3 peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide
 Clinical risk model: history of hypertension, diabetes, hyperlipidemia, waist circumference, and estimated glomerular filtration rate in addition to biomarker of interest

*FSTL3 and NT-proBNP were log-transformed in regression models for data normalization. OR for both biomarkers reflect 1-SD increase in log-transformed biomarker

Figure S1. Correlations of diastolic function and right heart pressures and function in metabolic heart disease Stage B pulmonary phenotype.



A: Mean e' and PASP relationship; **B:** RV/pulmonary circulation metrics and mean e' relationship