ORIGINAL RESEARCH

Impaired Right Ventricular Hemodynamics Indicate Preclinical Pulmonary Hypertension in Patients With Metabolic Syndrome

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***Background*—**Metabolic disease can lead to intrinsic pulmonary hypertension in experimental models. The contributions of metabolic syndrome (MetS) and obesity to pulmonary hypertension and right ventricular dysfunction in humans remain unclear. We investigated the association of MetS and obesity with right ventricular structure and function in patients without cardiovascular disease.

***Methods and Results*—**A total of 156 patients with MetS (mean age 44 years, 71% women, mean body mass index 40 kg/m^2), 45 similarly obese persons without MetS, and 45 nonobese controls underwent echocardiography, including pulsed wave Doppler measurement of pulmonary artery acceleration time (PAAT) and ejection time. Pulmonary artery systolic pressure was estimated from PAAT using validated equations. MetS was associated with lower tricuspid valve e′ (right ventricular diastolic function parameter), shorter PAAT, shorter ejection time, and larger pulmonary artery diameter compared with controls ($P<0.05$ for all). Estimated pulmonary artery systolic pressure based on PAAT was 42±12 mm Hg in participants with MetS compared with 32±9 and 32±10 mm Hg in obese and nonobese controls (P for ANOVA <0.0001). After adjustment for age, sex, hypertension, diabetes, body mass index, and triglycerides, MetS remained associated with a 20-ms–shorter PAAT (β=−20.4, SE=6.5, $P=0.002$ versus obese). This association persisted after accounting for left ventricular structure and function and after exclusion of participants with obstructive sleep apnea.

***Conclusions*—**MetS is associated with abnormal right ventricular and pulmonary artery hemodynamics, as shown by shorter PAAT and subclinical right ventricular diastolic dysfunction. Estimated pulmonary artery systolic pressures are higher in MetS and preclinical metabolic heart disease and raise the possibility that pulmonary hypertension contributes to the pathophysiology of metabolic heart disease. **(*J Am Heart Assoc*. 2015;4:e001597 doi: 10.1161/JAHA.114.001597)**

Key Words: echocardiography • metabolic syndrome • obesity • pulmonary hypertension

Metabolic disease and obesity are increasing in prevalence: The metabolic syndrome (MetS) affects approximately 30% of the US population in persons >20 years of age, and prevalence of MetS is 3 times higher in persons aged ≥40 years compared with those aged <40 years.[1,2] MetS as an entity has been shown to confer increased risk of incident heart failure.[3,4] In particular, many of the individual components of MetS have been strongly linked with the development of heart failure with preserved ejection fraction, which in turn strongly coexists with pulmonary hypertension.[5–7] Although MetS has been associated with subclinical diastolic dysfunction,[8,9] little is known about right ventricular (RV) function and pulmonary hemodynamics in obesity and metabolic disease. Previous experimental studies have demonstrated an association between metabolic disease and intrinsic pulmonary hypertension with regression of pulmonary vascular remodeling after targeting adiponectin and the peroxisome proliferator-activated receptor-γ pathways,[10,11] presenting compelling evidence that pulmonary hemodynamics may also be altered in metabolic heart disease.

We hypothesized that patients with MetS would show echocardiographic evidence of subclinical RV dysfunction and altered pulmonary hemodynamics when compared with both obese and nonobese controls. Furthermore, we sought to investigate whether changes in RV structure and function were related to underlying diastolic dysfunction. In the future,

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early detection of subclinical RV dysfunction and pulmonary hemodynamics in patients with metabolic disease may help identify those at high risk of developing heart failure and may provide an opportunity for disease prevention.

Methods

Study Sample

Participants with obesity and MetS were recruited consecutively from general cardiology, hypertension, obesity, and nutrition outpatient clinics at Boston Medical Center. MetS was defined as meeting ≥3 of the following 5 criteria: (1) increased waist circumference (≥102 cm for men or ≥88 cm for women), (2) increased fasting triglycerides (≥150 mg/dL), (3) high blood pressure (≥130/85 mm Hg) or antihypertensive therapy, (4) decreased high-density lipoprotein cholesterol (<40 mg/dL in men or, <50 mg/dL in women), (5) impaired fasting glucose (≥100 mg/dl).[12] Obesity without MetS was defined using body mass index (BMI) ≥30 kg/m^2 with 0 or 1 MetS criterion other than increased waist circumference. Nonobese controls with BMI <30 kg/m^2 and no major medical comorbidities were volunteers recruited at Boston Medical Center. Participants with clinically recognized cardiovascular disease (pulmonary hypertension, heart failure, coronary artery disease, valvular heart disease, angina, or atrial fibrillation) and those with asymptomatic left ventricular (LV) systolic dysfunction (LV ejection fraction <50% on any echocardiogram) were excluded from the study.

Clinical Assessment

All participants underwent a comprehensive medical history and physical examination. Anthropometrics, resting heart rate, blood pressure (obtained after 10 minutes of rest in a sitting position with 3 consecutive measurements averaged), and fasting blood work were obtained. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, and/or current antihypertensive therapy. Diabetes was defined as a fasting serum glucose level ≥126 mg/dL, and/or current medical therapy with an oral hypoglycemic agent and/or insulin. The study was approved by the Boston University Medical Center institutional review board. All participants provided informed consent prior to study enrollment.

Echocardiography

Two-dimensional transthoracic echocardiograms were performed with a 1- to 5-MHz transducer and a commercially available ultrasound machine (iE33; Phillips Medical Systems) by an experienced sonographer (A.P.). Studies were analyzed offline with a digital echo interface (Philips Xcelera) by a reader blinded to MetS status. Left atrial diameter, LV dimensions, relative wall thickness, and LV ejection fraction (using modified Simpson's method) were measured according to published recommendations.[13] LV mass was determined by the cubed method and indexed to height to the power of 2.7 to correct for body habitus.[14] Assessment of LV diastolic function included pulsed wave Doppler assessment of transmitral early (E) and late (A) inflow velocities, E/A ratio, E-wave deceleration time, and tissue Doppler imaging of myocardial velocities of both the medial and lateral mitral annulus.[15] Pulmonary capillary wedge pressure was estimated from the mitral E wave and tissue Doppler e′ (RV diastolic function parameter) velocity, as described previously.[16]

Right heart assessment was performed as outlined previously.[17] In brief, the right atrial area was determined from the apical 4-chamber view at ventricular end systole. RV basal diameter was determined from the apical 4-chamber view in end diastole, measuring the maximal short-axis dimension in the basal one-third of the right ventricle. Tricuspid annular plane systolic excursion was obtained by placing an M-mode cursor across the tricuspid annulus in a 4-chamber apical view and capturing the maximum annular movement during peak systole. Tissue Doppler imaging of the RV free wall in the 4-chamber apical view was performed by placing a sample volume in the tricuspid annulus or the middle of the basal portion of the RV free wall and measuring the tricuspid s′ (RV systolic function parameter) and e′ (RV diastolic function parameter) velocities. Pulsed wave Doppler interrogation of the pulmonary artery ejection with the sample volume at the pulmonary valve annulus determined RV ejection time and pulmonary artery acceleration time (PAAT). RV ejection time was the time interval measured from the onset to the cessation of pulmonary artery flow. PAAT was determined as the time measurement from onset of pulmonary arterial flow to the peak flow velocity.[18] Pulmonary artery diameter was measured in the proximal pulmonary artery in the parasternal short axis of the pulmonary bifurcation view. Calculation of the RV myocardial performance index, a global measurement of both systolic and diastolic function of the RV, was performed using tissue Doppler and defined as the ratio of tricuspid valve (TV) closure and opening time minus ejection time to ejection time.[17]

All echocardiographic measurements were averaged over 3 consecutive cardiac cycles (as available). Repeated measurements of 10 scans showed 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 measures. The intraobserver coefficient of variation for PAAT was 5.9%, and the interobserver coefficient of variation was 7.3%, with intraclass correlation coefficients ranging from 92% to 96%. A total of 14

participants were excluded because of inadequate quality of pulsed wave Doppler signal from the RV outflow tract to measure PAAT, leaving 246 participants (94.6%) with adequate images for analysis.

Statistical Analysis

Baseline clinical characteristics and echocardiographic characteristics were compared for the nonobese, obese, and MetS groups using 1-way ANOVA or chi-square statistics, as appropriate. Pairwise comparisons were subsequently performed using 2-sample *t* tests (continuous) and chi-square tests (categorical) with Bonferroni correction for multiple-comparison testing.

Differences in RV structure and function between the MetS and obese groups were assessed using multiple linear regression. Models were adjusted for age and sex, with subsequent addition of clinical covariates (systolic blood pressure, diabetes, body mass index, blood pressure treatment, and log-triglyceride concentrations) and then the addition of echocardiographic parameters of LV structure and function (including E/A ratio, mean e′ velocity, and LV mass). In secondary analyses, multivariable models were further adjusted for the presence of obstructive sleep apnea. A sensitivity analysis was conducted after excluding participants with obstructive sleep apnea (n=37).

Correlations of PAAT and other echocardiographic parameters of RV and LV structure and function in addition to clinical characteristics were assessed using pairwise Pearson correlation coefficients. In exploratory analyses, correlates of PAAT were investigated using forward and backward stepwise selection models, forcing age and sex, with covariate retention at $P<0.05$. Pulmonary artery systolic pressures were estimated from PAAT using a previously validated equation: $10^{([-0.04\times PAAT]+2.1)}$.[19] All analyses were performed using Stata release 11 (StataCorp).

Results

A total of 156 participants with MetS (44±11 years, 71% women) were compared with 45 obese participants without MetS (38±10 years, 89% women) and 45 nonobese controls (44±12 years, 73% women). Baseline clinical characteristics are displayed in Table 1. Participants with MetS had higher

Table 1. Baseline Characteristics in MetS, Obese, and Nonobese Groups

	Nonobese (n=45)	Obese (n=45)	MetS (n=156)	*P* Value
Clinical characteristics				
Age, y	44±12	38±10*	44±11†	0.006
Women, n (%)	33 (73)	40 (89)	111 (71)	0.05
White, n (%)	23 (51)	6 (13)*	47 (30)*†	0.001
Systolic blood pressure, mm Hg	111±13	119±11*	125±15*†	<0.001
Diastolic blood pressure, mm Hg	70±8	75±8*	78±10*	<0.001
Heart rate, beats per minute	62±10	68±9	72±2*	<0.001
Diabetes mellitus, n (%)	0 (0)	0 (0)	68 (44)*†	<0.001
Body mass index, kg/m^2	24±3	40±11*	40±9*	<0.001
Waist circumference, cm	82±14	111±19*	121±19*†	<0.001
Current smoker, n (%)	1 (2)	4 (9)	21 (13)	0.09
Obstructive sleep apnea, n (%)	0 (0)	4 (9)*	33 (21)*	0.002
Antihypertensive treatment, n (%)	0 (0)	9 (20)*	98 (63)*†	<0.001
Diabetes treatment, n (%)	0 (0)	0 (0)	61 (39)*†	<0.001
Statin treatment, n (%)	0 (0)	0 (0)	53 (34)*†	<0.001
Laboratory characteristics				
Total cholesterol, mg/dL	192±30	178±33	186±42	0.22
HDL cholesterol, mg/dL	59±13	50±10*	44±11*†	<0.001
Triglycerides, mg/dL	78±35	84±39	166±121*†	<0.001
Triglyceride/HDL ratio	1.5±0.9	1.8±1.0	4.2±3.6*†	<0.001
Creatinine, mg/dL	0.84 ±0.13	0.82 ±0.14	0.83±0.16	0.85

Values are mean±SD unless noted otherwise. HDL indicates high-density lipoprotein; MetS, metabolic syndrome.
*$P<0.05$ vs nonobese. †$P<0.05$ MetS vs obese.

systolic blood pressure and greater prevalence of obstructive sleep apnea compared with obese participants, but notably, BMI did not significantly differ between the 2 groups (P=0.52). Among participants with MetS, 44% had diabetes compared with none in the obese and nonobese groups. The triglyceride/high-density lipoprotein cholesterol ratio was significantly higher among participants with MetS and was comparable among obese and nonobese controls (4.2±3.6 in the MetS group versus 1.8±1.0 and 1.5±0.9 in the obese and nonobese groups, respectively).

Metabolic Syndrome Is Associated With Pulmonary Hypertension and RV Diastolic Dysfunction

No between-group differences were noted in right atrial or ventricular dimensions. Moreover, RV systolic function, as assessed by tricuspid annular plane systolic excursion and TV pulsed wave Doppler s′, was similar between groups (Table 2). In contrast, participants with MetS had a significantly shorter PAAT (123±32 ms, P for ANOVA <0.001) (Table 2) compared with the obese and nonobese control groups, whereas the latter 2 groups had similar PAAT (153±35 and 152±33 ms, respectively). In addition, MetS was associated with RV diastolic dysfunction, as demonstrated by a lower TV e′ and a lower TV e′/a′ ratio in comparison to the obese or nonobese groups (P for ANOVA ≤0.002 for both). In the MetS and obese groups, pulmonary artery diameter was larger and RV ejection time was shorter compared with nonobese controls. Larger pulmonary artery size appeared to persist even after indexing for aortic root size (Table 2).

Pulmonary artery systolic pressure was estimated using PAAT and a validated regression equation.[19] This showed that MetS was associated with a 10-mm Hg–higher pulmonary artery systolic pressure when compared with obese or nonobese controls (42±12 mm Hg in MetS compared with 32±9 and 32±10 mm Hg in the obese and nonobese groups, respectively; P for ANOVA <0.001) (Figure 1).

In addition to differences in right heart function and hemodynamics, as noted, participants with MetS had greater left atrial dimension, LV mass, and early diastolic dysfunction, as shown by lower mitral E/A ratio, lower mean e′, and higher E/e′ ratio compared with obese and nonobese participants (P for ANOVA <0.001 for all) (Table 2).

Differences in Estimated RV Hemodynamics Persist Despite Adjustment for LV Parameters

When comparing participants with MetS and those with obesity in the absence of MetS, differences in PAAT and RV diastolic dysfunction, as assessed by TV tissue Doppler e′ and e′/a′ ratio, persisted after accounting for age and sex, even with similar levels of BMI (Table 3). Furthermore, PAAT and the PAAT/ejection time ratio remained significantly lower in the MetS group compared with the obese group after accounting for clinical covariates, including blood pressure, BMI, diabetes, and log-triglycerides. Specifically, the presence of MetS was associated with a 20-ms–shorter PAAT after multivariable adjustment (β=−20.4, SE=6.5, P=0.002). Importantly, no attenuation of the differences in PAAT between the MetS and obese groups was noted after further adjustment for obstructive sleep apnea (β=−20.5, SE=6.6, P=0.002). In sensitivity analyses, results also remained robust after exclusion of participants with obstructive sleep apnea (n=37, multivariable-adjusted β=−19.9, SE=6.4, P=0.002) or with chronic obstructive pulmonary disease or asthma (n=59, multivariable-adjusted β=−9.6, SE=4.3, P=0.03).

After additional adjustment for LV parameters, including LV mass, E/A ratio, and mean e′ velocity, the difference in PAAT between groups persisted (β=−17.0, SE=6.7, P=0.01). This translated into a 5.6-mm Hg–higher estimated pulmonary artery systolic pressure in participants with MetS compared with obese participants after accounting for clinical and LV parameters (β=5.6, SE=2.4, P=0.02). When accounting for estimated pulmonary capillary wedge pressure in place of mean e′ velocity in multivariable analyses, PAAT remained shorter in those with MetS compared with obese participants (β=−17.7, SE=6.4, P=0.006).

Clinical and Echocardiographic Correlates of PAAT

When using the same PAAT cutoff of 110 ms as in previous studies (which corresponds to a pulmonary artery systolic pressure of 46 mm Hg),[20] the prevalence of mild to moderate pulmonary hypertension was 11% in the obese group and 36% in the MetS group (P=0.001). PAAT was modestly correlated with RV diastolic function in the MetS and obese groups (r=0.22, P=0.007 for TV e′; r=0.25, P=0.002 for TV e′/a′ ratio). Interestingly, there appeared to be a correlation of TV e′ and PAAT in the MetS group but not in the obese group (Figure 2). PAAT also correlated with LV diastolic function (r=0.30, P<0.001 for mitral valve mean e′; r=0.32, P<0.001 for mitral E/A ratio). Clinical correlates included abdominal adiposity as measured by waist circumference (r=−0.26, P<0.001) (Table 4).

In age- and sex-adjusted forward and backward selection models, multivariable-adjusted correlates of PAAT included MetS (P<0.001) and BMI (P=0.02) when clinical covariates were considered. When considering echocardiographic

Table 2. Echocardiographic Characteristics Among Nonobese, Obese, and MetS Groups

	Nonobese (n=45)	Obese (n=45)	MetS (n=156)	*P* for ANOVA
Right heart parameters				
RV basal diameter, mm	36±0.5	38±0.5	38±0.5	0.25
TAPSE, mm	23±4	24±4	23±4	0.15
RVOT diameter, mm	35±6	35±6	36±5	0.55
RVOT velocity, cm/s	85±13	87±16	93±17*	0.006
RVOT velocity time integral, cm	20±10	20±3	19±4	0.46
RV ejection time, ms	355±40	327±32*	333±42*	0.002
PAAT, ms	153±35	152±33	123±32*†	<0.001
PAAT/RV ejection time	0.43±0.11	0.47±0.10	0.37±0.11*†	<0.001
Right atrial area, cm^2	15±3	16±3	16±4	0.22
PA diameter, cm	2.0±0.3	2.3±0.4*	2.4±0.3*	<0.001
PA diameter/aortic root diameter	0.68±0.09	0.78±0.16*	0.79±0.14*	0.001
TV tissue Doppler s′, cm/s	12±1	13±2	13±2	0.31
TV tissue Doppler e′, cm/s	12±2	13±2	11±3*†	<0.001
TV tissue Doppler a′, cm/s	12±3	12±4	13±4	0.54
TV tissue Doppler e′/a′ ratio	1.1±0.3	1.2±0.4	0.9±0.3†	0.002
RV myocardial performance index	0.49±0.13	0.46±0.14	0.47±0.16	0.59
Estimated PASP, mm Hg	32±10	32±9	42±12*†	<0.001
Left heart parameters				
Left atrial diameter, mm	32±4	38±5*	38±5*	<0.001
Left atrial volume index, mL/m^2	33±9	37±9*	31±9†	<0.001
LVEDD, mm	46±4	48±5*	46±5†	0.02
LVEDD/height, mm/m	27.0±2.1	29.2±2.6*	27.5±2.8†	<0.001
LVESD, mm	30±4	32±4	30±5†	0.02
Posterior wall thickness, mm	8±1	10±2*	10±2*	<0.001
Interventricular septal thickness, mm	8±1	9±2*	10±2*	<0.001
Relative wall thickness	0.36±0.07	0.40±0.09*	0.44±0.08*†	<0.001
LV ejection fraction, %	63±6	61±4	63±6	0.33
LV mass/$height^{2.7}$, $g/m^{2.7}$	28±6	42±13*	40±10*	<0.001
Mitral E wave, cm/s	73±14	83±17*	78±18	0.02
Mitral A wave, cm/s	51±14	58±13	67±16*†	<0.001
Mitral E/A ratio	1.5±0.5	1.5±0.4	1.2±0.4*†	<0.001
Deceleration time, ms	198±33	191±26	197±35	0.50
Mean e′ wave, cm/s	11±3	12±2	9±2*†	<0.001
E/e′ ratio	7±2	7±2	9±2*†	<0.001
Estimated PCWP, mm Hg	10±2	11±2	13±3*†	<0.001

LV indicates left ventricle; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MetS, metabolic syndrome; PA, pulmonary artery; PAAT, pulmonary artery acceleration time; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; RV, right ventricle; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.
*P<0.05 vs nonobese. †P<0.05 MetS vs obese.

variables that had significant pairwise correlations, significant predictors included the E/A ratio (P=0.008) and relative wall thickness (P=0.04), although MetS status remained in the model despite adjustments for LV parameters (P<0.001) (Table 5). Mean e′ did not retain significance in multivariate modeling.

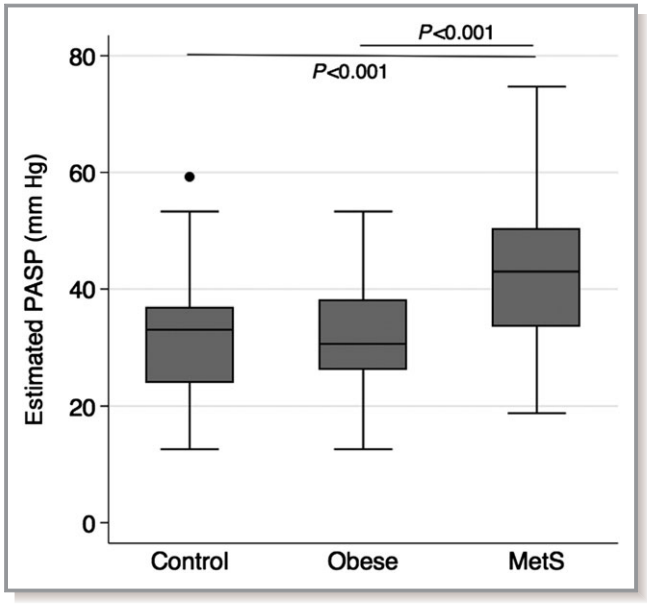

Figure 1. Estimated pulmonary artery systolic pressure (PASP) for nonobese controls, obese participants without metabolic syndrome, and participants with metabolic syndrome (MetS). *P* values represent pairwise comparisons. Box plot shows median value, 25th and 75th percentiles as lower and upper hinges, whiskers show upper and lower adjacent values, and dots represent outside values.

Table 3. Differences in Right Heart Parameters Between MetS and Obese Groups

	β (SE)*	*P* Value
Age- and sex-adjusted model		
PAAT	−25.5 (5.6)	<0.001
RVOT velocity	5.5 (2.9)	0.06
RV ejection time	8.9 (6.9)	0.20
PAAT/RV ejection time	−0.09 (0.02)	<0.001
PA diameter	0.07 (0.09)	0.44
PA diameter/Aortic diameter	0.03 (0.04)	0.37
TV tissue Doppler e′	−1.7 (0.50)	0.001
TV tissue Doppler e′/a′	−0.17 (0.07)	0.01
Multivariable-adjusted model*		
PAAT	−20.4 (6.5)	0.002
PAAT/RV ejection time	−0.08 (0.02)	<0.001
TV tissue Doppler e′	−0.80 (0.55)	0.15
TV tissue Doppler e′/a′	−0.10 (0.08)	0.22
Multivariable-adjusted model with LV parameters†		
PAAT	−17.0 (6.7)	0.01
PAAT/RV ejection time	−0.07 (0.02)	0.003

β estimate reflects differences in echocardiographic parameters between MetS and obese groups. LV indicates left ventricle; MetS, metabolic syndrome; PA, pulmonary artery; PAAT, pulmonary artery acceleration time; RV, right ventricle; RVOT, right ventricular outflow tract; TV, tricuspid valve.
*Multivariable-adjusted models included age, sex, systolic blood pressure, use of antihypertensive treatment, body mass index, diabetes, and log-triglycerides.
†Included clinical covariates and mitral E/A ratio, LV mean e′ velocity, and left ventricular mass.

Discussion

We found that MetS was associated with subclinical alterations in RV diastolic function and hemodynamics. Specifically, estimated pulmonary artery systolic pressures as assessed by PAAT were 10 mm Hg higher in participants with MetS compared with "metabolically healthy" obese participants with similar BMI. Notably, every 10-mm Hg increase in pulmonary pressures has been associated previously with a >2.7-fold increased risk of death, even in the absence of known cardiopulmonary disease, in the population-based Olmsted County cohort.[21] This result highlights the potential clinical importance of our findings in light of increasing rates of obesity and associated metabolic disease.[22] In secondary analyses, the association of MetS and PAAT was partly related to LV diastolic dysfunction including estimated pulmonary capillary wedge pressure; however, the association remained significant even after accounting for clinical risk factors and measures of LV function. This finding suggests that diastolic dysfunction may contribute to but may not entirely account for pulmonary hypertension observed in metabolic disease. Importantly, the association did not appear to be confounded by the presence of obstructive sleep apnea. Taken together, these findings raise the possibility that subclinical pulmonary hypertension plays a role in metabolic heart disease.

Few studies have characterized pulmonary artery pressures and RV structure and function across the spectrum of obesity and metabolic disease. Higher BMI has been associated with higher pulmonary pressures (estimated by tricuspid regurgitant jet velocity) in a large echocardiography-based cohort.[23] Pulmonary pressures, as estimated by PAAT, also correlated with BMI in the Coronary Artery Risk Development in Young Adults (CARDIA) study, in which the prevalence of mild–moderate pulmonary hypertension, as defined by a PAAT between 70.01 and 109.9 ms, was as high as 14%.[20] Interestingly, metabolic disease has been associated with pulmonary arterial hypertension[24] and pulmonary venous hypertension[25] in small studies of patients with symptomatic disease. We have extended these findings to a preclinical cohort of young participants without known cardiovascular disease and demonstrated that, at similar levels of obesity, those with metabolic disease had significantly higher estimated pulmonary arterial systolic pressures. The fact that we encountered differences in relatively young participants suggests that the effect of age-related changes in LV diastolic function are probably limited and supports the finding that pulmonary vascular remodeling appears to be independent of LV parameters.

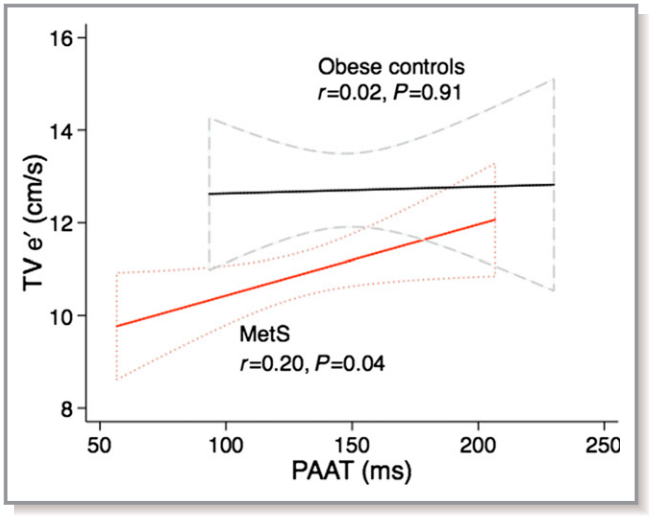

Figure 2. Association of pulmonary artery acceleration time (PAAT) and right ventricular diastolic function as assessed by tricuspid valve (TV) tissue Doppler e′ for participants with metabolic syndrome versus obese participants without metabolic syndrome.

Our finding of preclinical pulmonary hypertension in MetS is further bolstered by evidence of RV diastolic dysfunction. A few previous studies have examined RV function in relation to obesity. The Multi-Ethnic Study of Atherosclerosis (MESA) study showed that higher BMI was associated with greater RV mass, end-diastolic volumes, and stroke volume, even after accounting for LV parameters.[26] Obesity and MetS have also been associated previously with worse RV systolic and diastolic function, as assessed by tissue Doppler and strain imaging.[27–29] We have shown specifically that RV diastolic function is impaired in participants with MetS compared with metabolically healthy obese participants. Interestingly, those with MetS appeared to have worse RV diastolic function compared with obese controls and also have a steeper decline of RV diastolic function with a decrease in PAAT. This finding implies decreased compliance of both RV and pulmonary vasculature in MetS.

The mechanism by which metabolic disease may lead to pulmonary hypertension remains unclear, although previous experimental studies demonstrated that adiponectin deficiency, as is seen in obesity,[30] and alterations in multiple metabolic pathways[31] may be linked to pulmonary hypertension. In one study, apoE$^{-/-}$ mice fed a high-fat diet were noted to develop pulmonary arterial hypertension, with complete regression after treatment with rosiglitazone, a peroxisome proliferator-activated receptor-γ activator,[32] implicating the potential role of insulin resistance. Systemic endothelial cell dysfunction is well described in diabetes,[33] and pulmonary endothelial cells may be altered similarly in metabolic disease,[34] with reduced expression of peroxisome proliferator-activated receptor-γ,[35] E-selectin upregulation in the absence of adiponectin,[30] and increased inflammation and oxidative stress localized to lung tissue,[36] potentially leading to pulmonary vascular remodeling. This idea is supported by animal data showing that obese, insulin-resistant mice develop pulmonary vascular remodeling in the absence of changes in LV end-diastolic pressures.[36] This result supports our finding that the association of PAAT and metabolic disease persists even after adjustment for LV diastolic function measures, although our findings will have to be validated in future studies.

Table 4. Correlations of PAAT With Right Heart, Left Heart, and Clinical Parameters Between MetS and Obese Groups

	r	*P* Value
Right heart parameters		
Right heart basal diameter	−0.05	0.49
TAPSE	0.11	0.17
Right atrial area	−0.08	0.28
Right atrial major dimension	−0.10	0.17
Right atrial minor dimension	−0.09	0.24
PA diameter	0.12	0.26
RVOT velocity	−0.24	<0.001
RVOT velocity time integral	0.09	0.20
TV tissue Doppler e′, cm/s	0.22	0.007
TV tissue Doppler a′, cm/s	−0.15	0.08
TV tissue Doppler e′/a′ ratio	0.25	0.002
Left heart parameters		
Left atrial diameter	−0.05	0.49
Left atrial volume indexed to BSA	0.10	0.16
LVEDD	0.16	0.02
Relative wall thickness	−0.24	<0.001
LV ejection fraction	0.03	0.72
LV mass/height$^{2.7}$	0.02	0.73
Mean e′	0.30	<0.001
Mitral E/A ratio	0.32	<0.001
E/e′ ratio	−0.18	0.01
Clinical characteristics		
Age	−0.17	0.01
Systolic blood pressure	−0.15	0.04
Diastolic blood pressure	−0.08	0.28
Body mass index	−0.15	0.04
Triglyceride/HDL ratio	−0.15	0.04
Waist circumference	−0.26	<0.001

r denotes Pearson pairwise correlation coefficients. HDL indicates high-density lipoprotein; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; MetS, metabolic syndrome; PA, pulmonary artery; PAAT, pulmonary artery acceleration time; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; TV, tricuspid valve.

Table 5. Correlates of Pulmonary Artery Acceleration Time in Multivariable Analyses

Covariate	β (SE)	*P* Value
Clinical correlates		
Age	−0.38 (0.21)	0.08
Sex	11.3 (5.4)	0.036
MetS status	−24.2 (5.6)	<0.001
BMI	−0.59 (0.25)	0.02
Echo correlates		
Age	0.12 (0.24)	0.63
Sex	11.0 (5.3)	0.04
MetS status	−20.6 (5.6)	<0.001
E/A ratio	19.0 (7.1)	0.008
Relative wall thickness	−58.6 (27.7)	0.04

Backward and forward selection models, forcing age and sex, with covariate retention at $P<0.05$. Variables eligible for entry were selected based on pairwise correlations with $P<0.05$. In the clinical model, this included MetS status, systolic blood pressure, antihypertensive medications, body mass index, diabetes mellitus, and log-triglyceride concentrations. Variables eligible for entry in the echo model included MetS status, left ventricular end-diastolic dimension, relative wall thickness, mean e′, and E/A ratio. BMI indicates body mass index; MetS, metabolic syndrome.

The noninvasive assessment of pulmonary pressures focused previously on the tricuspid regurgitant jet velocity; however, only 15% of participants in a large echocardiography cohort study had measurable tricuspid regurgitant jets,[23] making this tool less useful in populations without overt cardiovascular disease. In contrast, PAAT can be obtained in the majority of cases and has been correlated with tricuspid regurgitant jet velocity and invasive pulmonary artery pressures in human studies[19,37,38] and in experimental models of pulmonary hypertension.[39,40] PAAT was measurable in the vast majority of participants in our study, whereas only 23% had measurable tricuspid regurgitant jets, supporting the use of PAAT as a potential screening measure for pulmonary hypertension in a preclinical population.

Several limitations deserve mention. Although the noninvasive estimation of pulmonary pressures using PAAT has been validated with invasively measured pressures in numerous studies, right heart catheterization remains the definitive modality by which to evaluate and diagnose pulmonary hypertension. Furthermore, we were unable to determine whether elevations in pulmonary pressures were the result of venous congestion in the setting of LV diastolic dysfunction or of intrinsic pulmonary vascular changes. This pathophysiological distinction will need to be clarified in future studies. In our multivariable analyses, the association of MetS and PAAT was attenuated in part when taking into account LV parameters; however, the association remained significant, suggesting that both pre- and postcapillary pulmonary hypertension may be involved. Although we were able to exclude participants with diagnosed obstructive sleep apnea, it is possible that undiagnosed sleep-disordered breathing may have influenced our results. Functional status was not formally assessed, although participants with clinically recognized cardiovascular disease and abnormal cardiovascular and pulmonary examinations were excluded from the study. Consequently, "preclinical" participants may have included those who were symptomatic but who remained clinically unrecognized. Last, less than a quarter of participants had adequate assessment of tricuspid regurgitant jet velocity by echocardiography to estimate pulmonary pressures, and this limited its use in our study. In the future, greater focus on ascertainment of tricuspid regurgitation and use of agitated saline to enhance assessment may be considered.

In summary, our findings support the presence of subclinical pulmonary hypertension and RV diastolic dysfunction in an asymptomatic cohort of participants with metabolic disease. Notably, when using the same PAAT cutoff of 110 ms as in previous studies (which corresponds to a pulmonary artery systolic pressure of 46 mm Hg),[20] the prevalence of mild to moderate pulmonary hypertension was 11% among our metabolically healthy obese group and 36% among our participants with MetS. Whether the presence of pulmonary hypertension is a harbinger of future heart failure risk in this population and the degree to which pulmonary hypertension is caused by intrinsic pulmonary vascular changes or is secondary to LV diastolic dysfunction remain to be elucidated. In light of the adverse prognosis associated with elevated pulmonary pressures, even in the absence of cardiopulmonary disease,[21] and the growing obesity epidemic and concomitant metabolic disease, perhaps an opportunity exists for future prevention and intervention. Future studies are needed to validate our findings and to further elucidate the mechanisms underlying pulmonary hypertension in metabolic disease.

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Disclosures

None.

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