

Association of Subclinical Right Ventricular Dysfunction With Obesity

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OBJECTIVES	The purpose of this research was to identify the determinants of right ventricular (RV) dysfunction in overweight and obese subjects.
BACKGROUND	Right ventricular dysfunction in obese subjects is usually ascribed to comorbid diseases, especially obstructive sleep apnea. We used tissue Doppler imaging to identify the determinants of RV dysfunction in overweight and obese subjects.
METHODS	Standard and tissue Doppler echocardiography was performed in 112 overweight (body mass index [BMI] 25 to 29.9 kg/m ²) or obese (BMI >30 kg/m ²) subjects and 36 referent (BMI <25 kg/m ²), including 22 with obstructive sleep apnea but no obesity. Tissue Doppler was used to measure RV systolic (s_m) and diastolic (e_m) velocities and strain indexes.
RESULTS	Obese subjects with BMI >35 kg/m ² had reduced RV function compared with referent subjects, evidenced by reduced s_m (6.5 ± 2.4 cm/s vs. 10.2 ± 1.5 cm/s, $p < 0.001$), peak strain ($-21 \pm 4\%$ vs. $-28 \pm 4\%$, $p < 0.001$), peak strain rate (-1.4 ± 0.4 s ⁻¹ vs. -2.0 ± 0.5 s ⁻¹ , $p < 0.001$), and e_m (-6.8 ± 2.4 cm/s vs. -10.3 ± 2.5 cm/s, $p < 0.001$), irrespective of the presence of sleep apnea. Similar but lesser degrees of reduced systolic function ($p < 0.05$) were present in overweight (BMI 25 to 29.9 kg/m ²) and mildly obese (BMI 30 to 35 kg/m ²) groups. Differences in RV e_m , s_m , and strain indexes were demonstrated between the severely versus overweight and mildly obese groups ($p < 0.05$). Body mass index remained independently related to RV changes after adjusting for age, log insulin, and mean arterial pressures. In obese patients, these changes were associated with reduced exercise capacity but not the duration of obesity and presence of sleep apnea or its severity.
CONCLUSIONS	Increasing BMI is associated with increasing severity of RV dysfunction in overweight and obese subjects without overt heart disease, independent of sleep apnea. (J Am Coll Cardiol 2006;47:611-6) © 2006 by the American College of Cardiology Foundation

The effect of excess weight on left ventricular (LV) morphology and function has been documented (1), but much less is known about the effects of obesity on right ventricular (RV) characteristics. Right ventricular changes have been attributed to obstructive sleep apnea (OSA) (2), which is highly prevalent in obese subjects, but the contribution of obesity to RV dysfunction is unclear.

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The assessment of RV function using M-mode or two-dimensional echocardiographic indexes is difficult due to its complex geometry. Radionuclide ventriculography, magnetic resonance imaging, and three-dimensional echocardiography can be used accurately to measure volumes and ejection fraction (3), but these indexes are load-dependent. Tissue Doppler imaging (TDI) allows measurement of systolic and diastolic myocardial velocities, has a more favorable signal-noise relationship, and permits the derivation of strain, which is a site-specific parameter. Long-axis velocities of the RV (free wall and tricuspid annulus) and strain indexes have been shown to be accurate and repro-

ducible measures of RV systolic function (4-6), and correlate well with the sonomicrometry (6). We used conventional echocardiographic, TDI, and strain indexes to determine whether RV dysfunction was associated with severity of OSA or body mass index (BMI) and identify the correlates of RV functional changes in a cohort of obese and non-obese subjects.

METHODS

Patient selection. We studied 148 subjects of both genders and divided into four groups based on degree of obesity: severely obese (BMI >35 kg/m², $n = 32$); mildly obese (BMI 30 to 34.9 kg/m², $n = 44$); overweight (BMI 25 to 29.9 kg/m², $n = 36$); and normal weight referent subjects (BMI <25 kg/m², $n = 36$). To examine the differential effects of sleep apnea and excess weight, we compared 22 consecutive subjects from our sleep laboratory who were non-obese (BMI <30 kg/m²) but had at least moderate OSA with 22 obese subjects (BMI >30 kg/m²) who all had confirmed sleep apnea on sleep studies, and a control group of 22 BMI-matched patients. To examine the effect of obesity alone, we compared 19 obese subjects without sleep apnea with the controls (Fig. 1). Obese subjects were recruited from general practice and specialist clinics based at a university hospital. Most of these patients had been involved in a previous study where we demonstrated LV

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Abbreviations and Acronyms

- AHI = apnea-hypopnea index
- BMI = body mass index
- LV = left ventricle/ventricular
- OSA = obstructive sleep apnea
- RV = right ventricle/ventricular
- RV e_m = right ventricular early diastolic velocity
- RV s_m = right ventricular systolic velocity
- SatO₂ = oxygen saturation
- SR = strain rate
- TDI = tissue Doppler imaging
- TR = tricuspid regurgitation
- VO₂max = peak ventilatory capacity

changes related to obesity (1). The referent group included healthy volunteers in the community.

Organic heart disease was excluded on the basis of a clinical assessment as well as resting and stress electrocardiogram and transthoracic echocardiography. We excluded subjects with ischemic heart disease, hypertension, and diabetes mellitus on the basis of previous history. Informed written consent for participation was obtained, and the hospital ethics committee approved the protocol.

Clinical assessment. Demographic details of age, gender, clinical status, and blood pressures were obtained from standard measurements and questionnaires. A detailed history and physical examination was conducted to exclude obesity-related and cardiovascular comorbidities. Arterial pressure was measured after subjects were rested for >5 min. Anthropometric and fat mass (tetrapolar bioelectrical impedance analyzer) measurements were obtained.

Biochemistry. Biochemical analysis of blood samples includes renal function, electrolytes, fasting insulin (Tosoh AIA-600 immunoassay, Tokyo, Japan), and lipid profile (enzymatic colorimetric assays).

Polysomnography. Sleep studies included measurements of sleep staging, ventilation, and oximetry for oxygen saturation (SatO₂) (Compumedics, Melbourne, Australia). Apneas were defined as a cessation of airflow for ≥10 s. Hypopnea was defined as a discrete reduction in any parameter of respiration of ≥10 s duration resulting in ≥3%

arterial oxygen desaturation or electroencephalographic arousal. The apnea-hypopnea index (AHI) is the total number of apneas or hypopneas per sleep hour, with an AHI of <5 within normal limits, and numbers of 5 to 15, 15 to 30, and >30 representing mild, moderate, and severe OSA, respectively. The average minimal and median SatO₂% readings were recorded.

Metabolic exercise testing. Treadmill exercise testing was performed using an exercise protocol individualized to the patient's exercise capacity. Peak ventilatory capacity (VO₂max) was obtained by breath-by-breath analyses of expired gas (V29C Sensormedics, Yorba Linda, California).

Echocardiography. Images were acquired using a standard ultrasound machine (Vivid 7, GE Vingmed, Horten, Norway) with a 2.5-MHz phased-array probe.

CONVENTIONAL ECHOCARDIOGRAPHY. Images were obtained in the parasternal long- and short-axis and apical four-chamber views. Left ventricular and RV diameter and wall thickness were measured from the M-mode tracings in the parasternal long axis (7); LV mass was determined by Devereux's formula, and indexed to height to the power of 2.7 (8).

Right ventricular end-diastolic and end-systolic volumes and the RV ejection fraction were computed from four-chamber views, using the area-length monoplane method ($V_{RV} = 3/8\pi[\text{area}^2/\text{length}]$). In patients where an adequate tricuspid regurgitation (TR) spectral Doppler profile was obtainable, pulmonary artery pressure was estimated from the sum of the modified Bernoulli equation ($[\text{TR jet velocity}]^2 \times 4$) and the estimated mean right atrial pressure.

TDI. Tissue Doppler imaging provides a number of sensitive parameters of systolic and diastolic function and also correlates with structural change, such as myocardial fibrosis (9). In each apical view, three cardiac cycles were recorded using color tissue Doppler at a high frame rate (120 MHz), giving a temporal resolution of 8 ms. The imaging angle was adjusted to ensure a parallel alignment of the beam with the myocardial segment of interest. Myocardial systolic velocity (s_m) and early diastolic velocity (e_m) were obtained at the

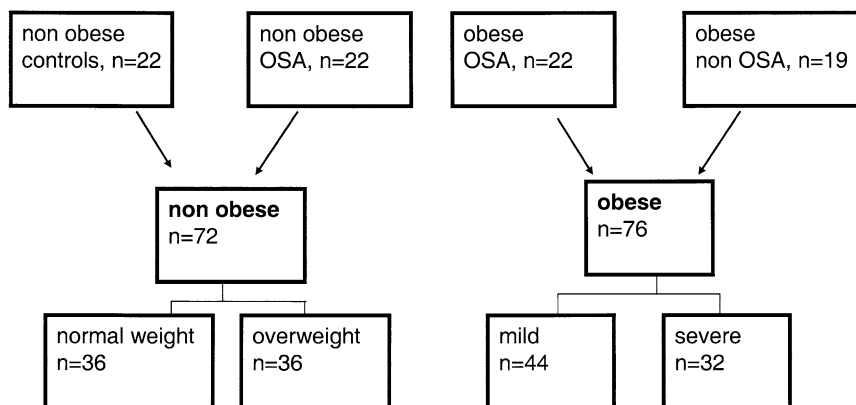


Figure 1. Grouping of subjects' selection. OSA = obstructive sleep apnea.

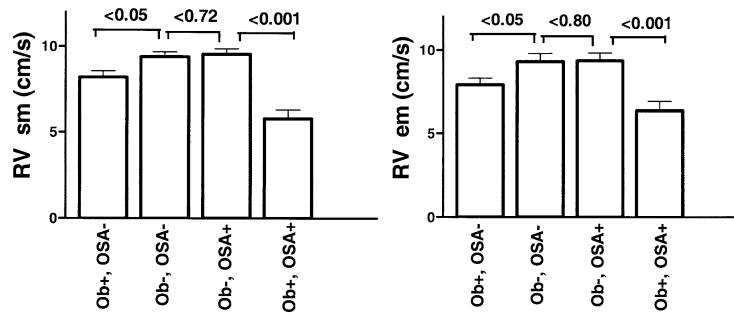


Figure 2. Differential effects of the presence of obstructive sleep apnea (OSA) and obesity (Ob) on (left) right ventricular (RV) s_m and (right) RV e_m in the four groups based on status of OSA and obesity.

basal RV free wall. Myocardial strain rate (SR; $\Delta V/\Delta t$) was derived between two points, where ΔV is the difference in velocity separated by a distance Δr . Strain (ϵ), the dimensionless relative change in length of the contracting muscle, is the temporal integral of the spatial differential of velocity $\int (\Delta V/\Delta r)\delta t$. Peak strain was defined as the greatest value on the strain curve (10,11). We have previously demonstrated the acquired signal is relatively independent of hemodynamic factors and LV cavity size (12).

Statistical analysis. Descriptive statistics are presented as mean \pm SD. Standard statistical analyses were used, including Pearson's correlations between BMI, echocardiographic variables, and sleep study parameters, and Spearman's correlation for insulin. Analysis of variance (ANOVA) was used to assess linear trends of parameters in the four groups, and post-hoc testing was undertaken using the Dunnett's multiple comparison tests. Independent *t* tests were used for comparison between subgroups based on the status of sleep apnea and obesity. Multivariate stepwise linear regression analysis was performed to assess the adjusted correlations between echocardiography variables and BMI. Parameters

that were not normally distributed (e.g., insulin) were log transformed into a normally distributed parameter for the regression model. Data were analyzed using standard statistical software (version 10, SPSS Inc., Chicago, Illinois). Probability values of $p < 0.05$ were considered significant.

RESULTS

Relationship between RV dysfunction and the presence and the severity of OSA. Figure 2 illustrates the RV s_m and e_m in subgroups defined by their sleep apnea and obesity status. Although not all patients had measurable TR jets, those with adequate TR signals—including those with significant OSA—did not have significantly elevated RV systolic pressure (>40 mm Hg) (Tables 1 and 2). While there were significant differences in the RV measures between the obese subjects with OSA (Ob+, OSA+; mean BMI = 47.3 kg/m², AHI = 40) and the reference group of non-obese subjects with moderate-to-severe OSA (Ob-, OSA+; mean BMI = 26.9 kg/m², AHI = 41; $p < 0.001$),

Table 1. Relationships of Severity of OSA With Echocardiographic Parameters of RV Characteristics in Subjects With OSA (Total n = 44)

	OSA Severity			ANOVA p Significance
	Mild n = 6	Moderate n = 18	Severe n = 20	
Age (yrs)	38	45	46	0.40
Weight (kg)	120 \pm 30	103 \pm 37	117 \pm 46	0.69
Height (m)	1.71 \pm 0.10	1.72 \pm 0.09	1.69 \pm 0.10	0.69
Gender (F/M)	4/2	5/13	8/12	0.25
BMI (kg/m ²)	40.9 \pm 10.0	35.6 \pm 14.5	37.2 \pm 13.8	0.71
Waist (cm)	125 \pm 7	112 \pm 28	120 \pm 34	0.62
PAP (mm Hg)	27 \pm 5	28 \pm 6	27 \pm 6	0.88
RV s_m (cm/s)	6.3 \pm 2.2	8.3 \pm 2.9	7.4 \pm 2.7	0.26
RV e_m (cm/s)	-7.0 \pm 2.6	-8.4 \pm 3.2	-7.6 \pm 2.5	0.52
RV strain ϵ (%)	-22.9 \pm 5.7	-27.4 \pm 5.5	-23.9 \pm 6	0.14
RV SR (s ⁻¹)	-1.3 \pm 0.4	-1.9 \pm 0.6	-1.7 \pm 0.4	0.09
Total AHI	9.5	21.2	63.3	<0.001
Total arousal index	17	24	56	<0.001
Average O ₂ saturation %	95	93	89	<0.05
Median O ₂ saturation %	95	96	91	0.06

AHI = apnea-hypopnea index; BMI = body mass index; e_m = myocardial early diastolic velocity; OSA = obstructive sleep apnea; PAP = pulmonary artery pressure; RV = right ventricular; s_m = myocardial systolic velocity; SR = strain rate.

Table 2. Clinical and Investigational Characteristics Include RV Characteristics (Morphology, Systolic and Diastolic Functions) in the Four Groups Categorized Based on BMI, compared by ANOVA

	Referent BMI <25 kg/m ² (n = 36)	Overweight BMI 25-29.9 kg/m ² (n = 36)	Mild Obesity BMI 30-34.9 kg/m ² (n = 44)	Severe Obesity BMI >35 kg/m ² (n = 32)	p
Age (yrs)	43 ± 11	44 ± 10	41 ± 8	44 ± 13	0.56
Weight (kg)	67 ± 9	87 ± 11	98 ± 11	132 ± 34	<0.001
Height (m)	1.71 ± 0.10	1.74 ± 0.10	1.73 ± 0.10	1.68 ± 0.10	0.07
Gender (F/M)	18/18	11/25	22/22	21/11	<0.05
Systolic BP (mm Hg)	121 ± 13	121 ± 14	119 ± 10	121 ± 16	0.85
Diastolic BP (mm Hg)	72 ± 9	79 ± 6	78 ± 10	78 ± 8	<0.05
BMI (kg/m ²)	22.9 ± 1.7	28.7 ± 2.0	32.5 ± 1.5	46.9 ± 11	<0.001
Waist (cm)	82 ± 6	95 ± 10	102 ± 9	134 ± 24	<0.001
Fat mass (%)	NA	28.8 ± 4.5	37.9 ± 6.1	49.4 ± 8.9	<0.001
Insulin (mU/l)	NA	7 ± 5	10 ± 10	25 ± 13	<0.001
VO ₂ max (ml/kg/min)	36 ± 7	37 ± 7	33 ± 8	17 ± 5	<0.001
RV FWT (mm)	33 ± 6	37 ± 6	38 ± 5	39 ± 9	<0.05
RV volume (ml)	35 ± 16	36 ± 13	38 ± 17	46 ± 18	<0.05
PAP (mm Hg)	27 ± 5	30 ± 6	29 ± 4	28 ± 8	0.80
RV ejection fraction (%)	54 ± 12	52 ± 11	53 ± 12	51 ± 11	0.77
RV s _m (cm/s)	10.2 ± 1.5	8.8 ± 2.0	8.3 ± 2.1	6.5 ± 2.4	<0.001
RV e _m (cm/s)	-10.3 ± 2.5	-8.9 ± 2.4	-8.3 ± 2.3	-6.8 ± 2.4	<0.001
RV strain ε (%)	-28.8 ± 4.2	-28.4 ± 4.6	-26.4 ± 4.4	-21.0 ± 4.5	<0.001
RV SR (s ⁻¹)	-2.0 ± 0.5	-1.9 ± 0.5	-1.8 ± 0.6	-1.4 ± 0.4	0.001
LVEDD (cm)	4.6 ± 0.5	4.8 ± 0.5	4.9 ± 0.5	5.0 ± 0.4	<0.05
LV mass/height ^{2.7} (kg/m ^{2.7})	31 ± 7	44 ± 10	46 ± 11	58 ± 17	<0.001

ANOVA = analysis of variance; BP = blood pressure; FWT = free wall thickness; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; PAP = pulmonary arterial pressure; other abbreviations as in Table 1.

myocardial measures were similar between the BMI-matched subjects (mean BMI = 26.4 kg/m²) without OSA (Ob-, OSA-) and the reference group who had OSA (Ob-, OSA+). Table 1 summarizes the clinical correlates of different degrees of severity of OSA in 44 subjects with positive sleep studies; no relationship was found between markers of sleep apnea severity with RV characteristics. Formal testing for interaction between obesity and OSA did not establish any such interaction.

Relationship between RV function and obesity. The effect of obesity on RV function (Fig. 2) was demonstrated by reduced RV function in obese subjects without sleep apnea (Ob+, OSA-, mean BMI = 38.1 kg/m²), in comparison with non-obese subjects without sleep apnea (Ob-, OSA-) (p < 0.05). Indeed, the degree of RV dysfunction progressively worsened in subgroups with progressive increases of BMI (Fig. 3).

Despite differences in diastolic (e_m) and systolic velocities (s_m) of the RV free wall among all three subgroups of obese subjects compared to the referents, RV ejection fraction did not differ between the subgroups, reflecting the insensitivity of ejection fraction in assessing early RV function. Similarly, there were differences in peak strain ε and SR among the obese subgroup though not all the comparisons with the referents reached statistical significance, probably due to wide standard deviation of the measured values due to signal noise. The reductions in RV function were matched by increasing RV chamber size and wall thickness with BMI (ANOVA, p < 0.05), as well as LV dilation and LV mass h^{2.7} index. These changes corresponded to increased cardiac

output (Table 2), reflecting volume loading in the adaptation to excess weight.

In the subgroups with increasing degrees of obesity, differences in weight and fat mass reflected categorization based on the BMI, but there was only a significant difference in diastolic blood pressure between the severely obese group and the referent group, even though none of the subjects had a diagnosis of hypertension. Indeed, BMI remained a significant predictor of RV s_m and RV e_m even after adjustment for age, log insulin, and mean arterial pressure in a multivariate stepwise regression model (β = -0.44, p < 0.01 and -0.40, p = 0.05, respectively) (Table 3).

Correlates of RV dysfunction in obesity. The important correlates for s_m and e_m were BMI, waist, and insulin, but not duration of obesity. Despite correlation of fasting insulin level with RV s_m (Spearman's rho = -0.45, p < 0.001) and e_m (Spearman's rho = -0.30, p < 0.05), there was close relationship between the fasting insulin level with BMI (rho = 0.72, p < 0.001). The relationship of RV function with insulin may therefore reflect correlation of the latter with BMI.

Relation to exercise capacity. Of those undergoing exercise testing, the RV s_m (r = 0.42, p < 0.001), RV ε (r = 0.65, p < 0.001), RV SR (r = 0.39, p < 0.001), and RV e_m (r = 0.32, p < 0.01) correlated with VO₂max.

Interobserver and intraobserver variability. Intraobserver differences were 0.2 ± 0.8 cm/s for tissue velocities, 1.6 ± 1.2% for ε, and 0.1 ± 0.1 s⁻¹ for SR. Interobserver differences were 0.3 ± 0.7 cm/s for tissue velocities, 1.8 ± 1.2% for ε, and 0.1 ± 0.1 s⁻¹ for SR.

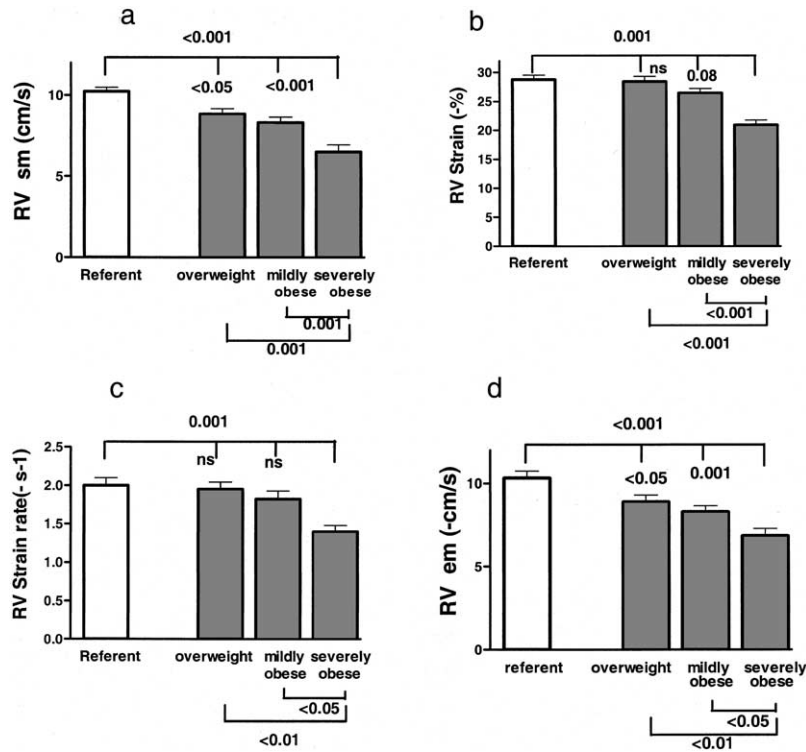


Figure 3. Relationship of body mass index with (a) right ventricular (RV) s_m , (b) peak strain ϵ , (c) peak strain rate, and (d) RV e_m in the four groups.

DISCUSSION

The results of this study show obese and overweight subjects who have no clinically appreciable respiratory conditions besides OSA have RV dilation and reduced RV longitudinal systolic and diastolic function. These changes were unrelated to the presence or the severity of OSA but appear related to the degree of obesity.

Previous studies of cardiac function in obesity. Earlier studies attributed RV changes in obesity preponderantly to sleep disordered breathing. In such patients, RV hypertrophy (13-15) and reduced RV ejection fraction (16,17) may be independent of pulmonary hypertension (16). However, the relative role of obesity and OSA in these previous studies was difficult to identify due to the significant overlap between obesity and OSA, and as indeed is the role of obesity relative to other covariates such as diabetes mellitus and hypertension (18). Interestingly, similar to our findings, RV dimensions and RV systolic function were not shown to be significantly different between subgroups with OSA of varied severity in the Framingham Heart study (13).

Potential mechanisms of RV dysfunction in obesity. Right ventricular functional changes in obese subjects are probably multifactorial. Right ventricular dilation (from intravascular volume overload) may increase myocardial oxygen consumption and ventricular wall stress (19). Second, although there was no independent effect of insulin resistance in this study, its effect on myocardial performance is still plausible. The metabolic effects of insulin resistance on myocyte function have been shown in vitro (20), and a clinical study also demonstrated its link with altered myocardial substrate metabolism and contractile function (21). Third, severe OSA may be responsible for hemodynamic disturbances as well as sympathetic nervous system activation after apnea termination (13), and these acute changes may lead to cardiovascular remodeling (22). Fourth, significant pulmonary hypertension would be expected to be an important influence on RV function, and despite our inability to detect significant pulmonary hypertension in those with an obtainable TR jet, incomplete data on pulmonary pressure remain an important limitation of the study.

Table 3. Independent Predictors of RV s_m and RV e_m in Overweight and Obese Patients

	RV s_m ($R^2 = 0.31$)		RV e_m ($R^2 = 0.26$)	
	β	p	β	p
Age	-0.15 (-0.11 to 0.02)	0.14	-0.30 (-0.17 to -0.02)	<0.05
BMI	-0.44 (-0.15 to -0.04)	<0.01	-0.41 (-0.18 to -0.03)	<0.05
Arterial pressure	0.13 (-0.02 to 0.08)	0.23	0.10 (-0.04 to 0.10)	0.27
Log insulin	-0.17 (-1.40 to 0.25)	0.17	-0.05 (-1.23 to 0.99)	0.20

Abbreviations as in Table 1.

Association of RV and LV dysfunction in obesity. Similar reports of reduced tissue velocity in the LV myocardium (1) likely reflect the systemic nature of the underlying pathophysiology, both in terms of preload and metabolic effects. An exception regarding ventricular interaction relates to circumstances when LV performance may be affected by displacement of the interventricular septum from elevated RV volume or pressure (23). Similarly elevated LV filling pressure can translate to elevated RV pressure and hence RV abnormalities, but it is less plausible that such interaction exists with subclinical LV dysfunction. Interestingly, although duration of obesity is a predictor of LV mass and LV diastolic function, it was not associated with RV characteristics.

Conclusions. This study demonstrates the presence of subclinical RV dysfunction in patients with overweight and obesity that was not explained by OSA, diabetes, hypertension, or other comorbidities. Such early RV changes are related to the degree of obesity and functional capacity and independent of presence of sleep-disordered breathing or its severity. The possible metabolic associations of these myocardial changes warrant further investigation by examining the response to various therapies, including weight loss and treatment of insulin resistance. Finally, TDI, which has a more robust signal-to-noise ratio compared to strain imaging, may provide a useful tool to monitor the disease process and treatment response of this subclinical myocardial dysfunction.

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