Obesity and Right Ventricular Structure and Function

The MESA-Right Ventricle Study

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Background: The relationship between obesity and right ventricular (RV) morphology is not well studied. We aimed to determine the association between obesity and RV structure and function in a large multiethnic population-based cohort.

Methods: The MESA-Right Ventricle Study measured RV mass and volumes by cardiac MRI in participants aged 45 to 84 years without clinical cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis (MESA). Participants were divided into three categories based on BMI: lean (≤ 24.9 kg/m²), overweight (25-29.9 kg/m²), and obese (≥ 30 kg/m²).

Results: The study sample included 4,127 participants. After adjustment for demographics, height, education, and cardiovascular risk factors, overweight and obese participants had greater RV mass (6% and 9% greater, respectively), larger RV end-diastolic volume (8% and 18% greater, respectively), larger RV stroke volume (7% and 16% greater, respectively), and lower RV ejection fraction ($\geq 1\%$ lower) than lean participants (all $P < .001$). These findings persisted after adjusting for the respective left ventricular (LV) parameters.

Conclusions: Overweight and obesity were independently associated with differences in RV morphology even after adjustment for the respective LV measure. This association could be explained by increased RV afterload, increased blood volume, hormonal effects, or direct obesity-related myocardial effects.

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Abbreviations: LV = left ventricle; LVEF = left ventricular ejection fraction; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVSV = right ventricular stroke volume; SDB = sleep-disordered breathing

The prevalence of obesity has doubled in adults and more than tripled in children in the United States in the past 25 years and increases the risk of heart failure and death.^{1,2} Obesity is associated with increases in total blood volume, left ventricular (LV) mass, LV stroke volume, and cardiac output without changes in LV ejection fraction (LVEF).³⁻⁷ Also seen is the direct infiltration or metaplasia of fat in the heart, termed the “cardiomyopathy of obesity.”⁸⁻¹⁰

Right ventricular (RV) morphology and function are important determinants of outcome in cardiopulmonary conditions, such as COPD, congestive heart failure, and pulmonary arterial hypertension.¹¹⁻¹³ Although obesity clearly affects the LV, few studies

have examined the impact of obesity on the RV. Studies have shown RV systolic and diastolic dysfunction in overweight and obese individuals.^{14,15} However, these were small studies of selected populations without significant ethnic diversity using transthoracic echocardiography, which has limitations in the evaluation of the RV particularly in obese individuals. MRI offers precise and reproducible assessment of the RV and is considered the standard of reference for determination of RV morphology.¹⁶ The aim of this study was to assess the relationship between obesity and RV structure and function assessed with MRI in a multiethnic population free of clinical cardiovascular disease.

MATERIAL AND METHODS

Study Population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter prospective cohort study designed to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in individuals without previous clinical cardiovascular disease (e-Appendix 1).¹⁷ The participants of MESA were 6,814 men and women age 45–84 years old who were white, African American, Hispanic, or Chinese. Exclusion criteria included clinical cardiovascular disease, current atrial fibrillation, any cardiovascular procedure, pregnancy, active cancer treatment, weight > 136 kg (300 lb), and serious medical condition that precluded long-term participation. The protocols of MESA and all studies described herein were approved by the institutional review board of the University of Pennsylvania (#808374) and the other collaborating institutions. The MESA-Right Ventricle Study is an ancillary study supported by a National Institutes of Health grant that planned for the selection of 4,634 participants with interpretable cardiac MRIs at the baseline examination for measurement of RV morphology, which was completed in 4,204 (Fig 1). Participants were sampled without regard to demographics, anthropometrics, or other clinical variables.

Cardiac MRI Measures

The cardiac MRI protocol and methods for interpretation of LV and RV parameters have been reported (e-Appendix 1).^{18,19} The intra-reader and interreader intraclass correlation coefficients from random, blinded re-reads were > 0.90 for all parameters except for RV ejection fraction (RVEF), for which they were ≥ 0.80.²⁰

Measurement of Body Size and Obesity

Height was measured to the nearest 0.1 cm with the subject in stocking feet. Weight was measured to the nearest 0.5 kg with the subject in light clothing using a balanced scale. BMI was calcu-

lated (weight [kg]/height [m]²). Overweight and obesity were defined as BMI between 25 and 29.9 kg/m² and ≥ 30 kg/m², respectively. Those with BMI < 25 kg/m² were considered “lean.” Waist circumference was measured to the nearest 0.1 cm using a steel measuring tape (standard 4-oz tension) from midway between the last rib and the iliac crest at normal breathing. Hip circumference was measured to the nearest 0.1 cm from the largest diameter of the hip.

Covariates

See e-Appendix 1 for details. Spirometry measures were available for a subset of participants (n = 2,755).²¹

Statistical Analysis

See e-Appendix 1 for details. Statistical significance was defined as $P < .05$. Analyses were performed using STATA 10.1 (StataCorp).

RESULTS

There were 6,814 men and women enrolled in MESA (Fig 1). Of them, 5,098 underwent cardiac MRI and 5,004 (98%) had interpretable examinations for the LV. We successfully interpreted 4,204 (of 4,634 selected) for RV measures (91%). Seventy-seven participants were excluded due to missing covariates, leaving 4,127 in the study sample and 2,687 excluded (Fig 1). The mean age was 61.5 years, 47% were men, 39.3% were white, 26.2% were African American, 22% were Hispanic, and 12.5% were Chinese. As compared with the excluded participants, the study sample was slightly younger (61.5 vs 63.2 years), had a lower BMI (27.9 vs 29.1 kg/m²), and had a lower systolic BP (125.5 vs 128.4 mm Hg).

Table 1 shows descriptive data by BMI categories. The ages of the three groups were similar. Overweight participants were somewhat more likely to be men and obese participants to be women. Overweight and obese participants were more likely to be African American or Hispanic, were less likely to be Chinese, and had lower levels of educational attainment. Overweight and obese participants were more likely to be hypertensive, to have impaired fasting glucose and diabetes, and to use antihypertensive therapy and lipid-lowering medications.

The adjusted least squares mean values for RV mass, volumes, and RVEF within each weight category are shown in Table 2. RV mass and volumes were greater in overweight and obese participants as compared with the lean participants after adjusting for demographic factors and other covariates ($P < .001$). RV mass was 6% higher in overweight participants and 14% higher in obese participants compared with lean participants. Even after adjustment for LV mass, obese participants still had 8% greater RV mass than lean participants ($P < .001$). Fully adjusted and LV-adjusted RV end-diastolic

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FIGURE 1. Study population. LV = left ventricle; MESA = Multi-Ethnic Study of Atherosclerosis; RV = right ventricle.

volume (RVEDV) results were similar (or greater) in magnitude to those of RV mass. Fully-adjusted RV stroke volume (RVSV) was 7% larger in overweight and 16% larger in obese participants compared with lean individuals ($P < .001$). We did not adjust for LV stroke volume considering the dependence of this measure on RVSV. RVEF was slightly but significantly lower in the overweight and obese

participants as compared with the lean group ($P < .001$), which remained significant even after adjusting for risk factors and LVEF ($P = .001$).

Modeled as a continuous variable, BMI was significantly (and linearly) associated with RV parameters after adjusting for age, sex, race/ethnicity, height, education, and other variables from the full models in Table 2. A 5 kg/m² increase in BMI was associated with a 1.3 g higher RV mass (Fig 2), 8.65 mL higher RVEDV, 5.55 mL higher RVSV, and 0.5% lower RVEF (all $P < .001$).

Figure 3 shows the results from generalized additive models for the relationship between standardized RV mass and BMI after adjustment for RVEDV and other covariates (as well as a similar model for the LV). This analysis is essentially identical to (and makes fewer analytic and morphologic assumptions than) examining the relationship of BMI with RV mass/RVEDV. There was a proportional increase in RV mass and RVEDV with increasing BMI in lean participants (represented by the flat portion of the black line of Figure 3 running from BMI 15 to ~25 kg/m²). However, there was a positive slope of the line with higher BMI in overweight and obese participants

Table 1—Characteristics of the Study Sample (N = 4,127)

Characteristic	BMI Categories		
	Lean BMI ≤ 24.9 kg/m ² (n = 1,255)	Overweight BMI 25-29.9 kg/m ² (n = 1,657)	Obese BMI ≥ 30.0 kg/m ² (n = 1,215)
Age, y	61.9 $\pm$ 10.5	62.1 $\pm$ 10.1	60.2 $\pm$ 9.5
Male, %	44.9	54.1	40.8
Race/ethnicity, %			
White	42.8	40.7	33.7
African American	16.9	24.9	37.5
Hispanic	12.7	25.2	27.2
Chinese	27.6	9.2	1.6
Education, %			
< High school	13.6	18.2	16.4
High school	16.5	18.7	20.1
< College, (> high school)	26.9	26.0	33.5
$\geq$ College	43.0	37.1	30.0
Height, cm	165.7 $\pm$ 9.7	167.4 $\pm$ 10.1	165.6 $\pm$ 9.9
Weight, kg	62.3 $\pm$ 9.4	77.2 $\pm$ 10.3	93.2 $\pm$ 13.1
BMI, kg/m ²	22.6 $\pm$ 1.8	27.4 $\pm$ 1.4	33.9 $\pm$ 3.5
Hypertension, %	31.0	44.9	52.4
Systolic BP, mm Hg	120.6 $\pm$ 21.4	126.6 $\pm$ 20.7	129.0 $\pm$ 20.1
Diabetes mellitus, %			
Normal	85.5	74.3	65.8
Impaired fasting glucose	8.0	14.4	16.9
Diabetes (treated/untreated)	6.5	11.3	17.3
Total cholesterol, mg/dL	193.6 $\pm$ 33.6	195.0 $\pm$ 35.2	194.2 $\pm$ 36.3
Antihypertensive medication use, %	23.6	37.6	46.0
Lipid-lowering medicine use, %	12.2	17.9	18.0
Smoking status, %			
Never smoker	54.9	50.6	51.6
Former smoker	33.1	36.0	36.7
Current smoker	12.0	13.4	11.7
Pack-y (among ever smokers)	21.3 $\pm$ 24.9	22.7 $\pm$ 25.4	24.3 $\pm$ 35.0

Table 2—Adjusted Least Square Mean Values of RV Parameters Within Each BMI Category

Parameter	Weight Status			P for Trend
	Lean BMI ≤ 24.9 kg/m ² (n = 1,255)	Overweight BMI 25-29.9 kg/m ² (n = 1,657)	Obese BMI ≥ 30.0 kg/m ² (n = 1,215)	
RV end-diastolic mass, g				
Model including age, sex, race/ethnicity, height	19.2	20.4	22.0	< .001
Full model	19.2	20.4	22.0	< .001
Full model + LV end-diastolic mass	20.7	21.4	22.3	< .001
RV end-diastolic volume, mL				
Model including age, sex, race/ethnicity, height	108.6	116.7	127.7	< .001
Full model	107.8	116.2	127.4	< .001
Full model + LV end-diastolic volume	114.7	118.6	123.8	< .001
RV stroke volume, mL				
Model including age, sex, race/ethnicity, height	78.4	83.7	91.0	< .001
Full model	78.0	83.4	91.0	< .001
RV ejection fraction, %				
Model including age, sex, race/ethnicity, height	72.6	72.2	71.8	< .001
Full model	72.9	72.5	71.9	.001
Full model + LV ejection fraction	72.3	71.9	71.4	.001

Full model includes: age, sex, race/ethnicity, height, education, systolic BP, cigarette smoking, pack-years, total cholesterol, diabetes and impaired fasting glucose, antihypertensive medication, and lipid-lowering medication. LV = left ventricle; RV = right ventricle.

(BMI > 25 kg/m²), indicating that there was a BMI-related increase in RV mass out of proportion to RVEDV in these subjects (P for nonlinearity = .03). This association contrasted with that of BMI with LV mass after adjustment for LV end-diastolic volume (LVEDV), which showed disproportionate increases of mass to volume with increasing BMI in lean participants with smaller increases in obese individuals (P for nonlinearity $< .001$). There were no interac-

tions of weight status or BMI with demographics in any of these analyses.

The associations between weight status or BMI and RV parameters were not altered by adjustment for FEV₁/FVC in those participants with available spirometry (n = 2,755) (e-Table 1). In the same subsample, exclusion of those subjects with restrictive ventilatory defects (FVC $<$ lower limit of normal with FEV₁/FVC > 0.70) or obstructive ventilatory defects (FEV₁/FVC < 0.70) did not change the results (e-Table 2). We performed additional analyses in the 748 individuals with complete sleep questionnaires (138 with possible sleep-disordered breathing [SDB] and 610 without SDB). In this subset, adjustment for the presence of SDB in the multivariate models of weight status and BMI with RV parameters did not significant change any of the results (e-Table 3).

Greater waist circumference and waist to hip ratio were significantly associated with increased RV mass and volumes, even after adjustment for the respective LV parameter (Table 3). RVEF showed an inverse relationship with both waist circumference and waist to hip ratio both before and after adjusting for LVEF.

DISCUSSION

In a community-based population free of clinical cardiovascular disease, overweight and obese individuals had greater RV mass and larger RV volumes than lean participants, whereas RVEF was slightly lower in

FIGURE 2. Scatterplot and running line smoother (solid line) with 95% CI (dashed lines) of the association between BMI and RV mass after adjusting for age, sex, race/ethnicity, height, education, systolic BP, cigarette smoking, pack-years, total cholesterol, diabetes and impaired fasting glucose, antihypertensive medication, and lipid-lowering medication ($P < .001$). See Figure 1 legend for expansion of abbreviation.

FIGURE 3. Generalized additive model of the association between BMI and standardized RV mass (black line) and 95% CI (dashed lines) after adjusting for age, sex, race/ethnicity, height, education, systolic BP, cigarette smoking, pack-years, total cholesterol, diabetes and impaired fasting glucose, antihypertensive medication, lipid-lowering medication, and right ventricular end-diastolic volume (P for nonlinearity = .03). For comparison, the association between BMI and standardized LV mass (gray line) after adjusting for age, sex, race/ethnicity, height, education, systolic BP, cigarette smoking, pack-years, total cholesterol, diabetes and impaired fasting glucose, antihypertensive medication, lipid-lowering medication, and LV end-diastolic volume is shown (P for nonlinearity < .001). A proportional increase in ventricular mass and end-diastolic volumes with increasing BMI should appear as a horizontal line. See Figure 1 legend for expansion of abbreviations.

heavier individuals. Although a generalized cardiac adaptation to larger body size could explain these findings, the results were adjusted for height and were only moderately attenuated by adjustment for the respective LV parameters, making this less likely. BMI and measures of abdominal obesity showed linear associations with RV parameters consistent with the results using weight status. In overweight individuals, there was a nonlinear increase in RV mass out of proportion to RVEDV related to higher BMI.

These associations persisted despite adjustment for spirometry measures and the presence of SDB. This study overcomes limitations of prior studies by using MRI in a very large community-based population of older adults and suggests that obesity-associated RV changes could have clinical implications. Weight loss interventions in overweight patients with RV dysfunction could affect RV morphology; however, studies of this approach have not been performed.

Previous echocardiographic studies have shown both systolic and diastolic RV dysfunction in the obese.^{14,22} Wong et al¹⁴ showed that overweight and obese individuals had lower RV free wall strain and strain rate (ie, worse function) and greater RV free wall thickness and volume compared with lean individuals (mean age, ~44 years; $n = 148$), even in those without SDB. Using MRI, Danias et al²³ showed greater RV mass and larger RVEDV and RVSV in 25 obese men compared with 25 lean men (mean age, ~30 years), all without medical comorbidities (including hypertension, diabetes mellitus, and SDB). These findings did not persist after accounting for height, although small sample sizes might have limited power. Our results were independent of indicators of body size (such as height or the respective LV parameter) and medical comorbidities. Thus, these associations between obesity and RV morphology cannot be simply attributed to the presence of hypertension, diabetes mellitus, or other sequelae.

The cardiac effects of obesity may occur through several mechanisms.⁴ First, obesity-related increased blood volume results in increased stroke volume and cardiac output, which chronically affect ventricular mass and volumes.⁶ Second, subclinical or episodic hypoxemia (such as during activity or sleep) may directly affect the RV.²⁴ Third, increased RV afterload may result from SDB-related hypoxic vasoconstriction.

Table 3—Associations Between Measures of Abdominal Obesity and RV Parameters

Obesity Measure	Parameter	Full Model			Full Model + LV Parameter		
		β	SE	P Value	β	SE	P Value
Waist circumference (per 10-cm increase)	RV end-diastolic mass, g	0.7	0.04	< .001	0.4	0.04	< .001
	RV end-diastolic volume, mL	4.6	0.3	< .001	2.1	0.2	< .001
	RV stroke volume, mL	2.9	0.2	< .001	...	...	...
	RV ejection fraction, %	−0.3	0.1	.001	−0.3	0.1	< .001
Waist to hip ratio (per 0.1 increase)	RV end-diastolic mass, g	0.5	0.1	< .001	0.2	0.1	< .001
	RV end-diastolic volume, mL	2.7	0.5	< .001	1.6	0.4	< .001
	RV stroke volume, mL	1.4	0.4	< .001	...	...	...
	RV ejection fraction, %	−0.4	0.1	.003	−0.4	0.1	.001

Full model adjusted for age, sex, race/ethnicity, height, education, systolic BP, cigarette smoking, pack-years, total cholesterol, diabetes mellitus and impaired fasting glucose, antihypertensive medication, and lipid-lowering medication. See Table 2 legend for expansion of abbreviations.

tion, a restrictive ventilatory defect, or LV dysfunction (systolic or diastolic). Fourth, obesity is associated with changes in adipokine levels, which have an effect on ventricular morphology.^{25,26} Finally, studies have identified the common occurrence of fatty infiltration of the RV.²⁷ A histopathologic study of 148 hearts from individuals who had died of noncardiac causes found intramyocardial fat in 85% of the hearts examined, with the highest amount of RV fat in the lateral wall.²⁸ A study of 49 subjects using enhanced CT imaging showed that obesity was a significant risk factor for fat replacement of the RV myocardium in healthy individuals.²⁹ Animal models of cardiac-specific steatosis show an increase in cardiac mass, ventricular dilation, and progression to heart failure in the absence of systemic obesity or its sequelae, suggesting a direct cardiotoxic effect of fat.³⁰ Human studies have shown that myocardial lipid content increases with BMI³¹ and contributes to oxidative stress and cardiac myocyte apoptosis.

In MESA, as in other studies, obesity was associated with greater LV mass, larger LV volumes, and preserved LVEF.^{5,32,33} In our study, the associations between weight status and RV parameters were attenuated but remained statistically and clinically significant after adjusting for the corresponding LV parameters, suggesting that the RV changes go beyond a nonspecific biventricular response to increased body size. That is, simple increased metabolic demand or volume changes do not fully explain our findings, as these associations would otherwise have been abolished (or greatly diminished) by adjustment for LV parameters. Therefore, our results not only suggest weight-related changes in the RV but also indicate that the processes responsible may be distinct (or independent) from those affecting the LV. For example, LV diastolic dysfunction is associated with increased LV mass; however, we found RV changes independent of LV variables. In fact, the morphologic pattern of RV mass to RVEDV relative to increasing BMI was very different from that demonstrated for the LV.

It is not known whether these obesity-related RV changes are adaptive or maladaptive. Although increased mass and volumes could arguably be compensatory, decreased RVEF (even minimally) is less convincingly an “adaptive” response. Weight loss in obese patients leads to improvement in RV myocardial performance index.³⁴ Furthermore, weight reduction improves the synchrony between the right and left ventricles and ameliorates RV morphologic changes, improving RV function.^{35,36} Therefore, RV changes could contribute to the increased risk of clinical heart failure associated with obesity. Studies of weight loss interventions in patients with cardiopulmonary disease should focus on RV morphologic end points.

This study has some limitations. Comorbidities could confound or mediate the associations between weight status and RV structure and function; however, we performed extensive multivariate adjustment with persistence of the associations of significant magnitudes, making this less likely. The study sample was limited to those free of clinical cardiovascular disease (but including individuals with hypertension and diabetes mellitus, which were not considered clinical cardiovascular diseases in MESA by design), limiting inferences to this group. Invasive pulmonary hemodynamic measurements are an important determinant of RV function but were of course not feasible in 4,000 healthy community-based participants and were not available. Echocardiographic or MRI measures of pulmonary artery pressures were also unavailable. We did not have a measure of LV diastolic dysfunction, which could account for some of the findings; however, the persistence of the associations even with adjustment for LV mass and the presence of hypertension makes this less likely. SDB was not assessed with polysomnography, and the sensitivity and specificity of the questions used are not clear, so residual confounding could be present.³⁷⁻⁴⁰ MESA excluded individuals with weight >300 pounds, so that morbidly obese individuals in the study may have been less than those in the general population. Finally, this is a cross-sectional study, which cannot assess temporality or prove causality. It is unknown whether weight loss would reverse the effects on the RV.

In conclusion, overweight and obese individuals without clinical cardiovascular disease demonstrate increased RV mass, larger RV volumes, and reduced RVEF, independent of pulmonary function, other comorbidities, and respective changes in the LV. Future studies should explore the mechanisms of these changes and evaluate the effect of weight loss therapies on the RV.

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Additional information: The e-Appendix and e-Tables can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/141/2/388/suppl/DC1>.

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