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STRUCTURE AND FUNCTION

Cardiac Structure and Function in the Obese: A Cardiovascular Magnetic Resonance Imaging Study

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ABSTRACT

Background. Obesity is a major health problem in the Western world. Among obese subjects cardiac pathology is common, but conventional noninvasive imaging modalities are often suboptimal for detailed evaluation of cardiac structure and function. We investigated whether cardiovascular magnetic resonance imaging (CMR) can better characterize possible cardiac abnormalities associated with obesity, in the absence of other confounding comorbidities. *Methods*. In this prospective cross-sectional study, CMR was used to quantify left and right ventricular volumes, ejection fraction, mass, cardiac output, and apical left ventricular rotation in 25 clinically healthy obese men and 25 age-matched lean controls. *Results*. Obese subjects had higher left ventricular mass (203 ± 38 g vs. 163 ± 22 g, $p < 0.001$), end-diastolic volume (176 ± 29 mL vs. 156 ± 25 mL, $p < 0.05$), and cardiac output (8.2 ± 1.2 L/min vs. 6.4 ± 1.3 L/min, $p < 0.001$). The obese also had increased right ventricular mass (105 ± 25 g vs. 87 ± 18 g, $p < 0.005$) and end-diastolic volume (179 ± 36 mL vs. 155 ± 28 mL, $p < 0.05$). When indexed for height, differences in left and right ventricular mass, and left ventricular end-diastolic volume remained significant. Apical left ventricular rotation and rotational velocity patterns were also different between obese and lean subjects. *Conclusions*. Obesity is independently associated with remodeling of the heart. Cardiovascular magnetic resonance imaging identifies subtle cardiac abnormalities and may be the preferred imaging technique to evaluate cardiac structure and function in the obese.

Key Words: Cardiovascular magnetic resonance (CMR); Obesity; Tagging.

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INTRODUCTION

Obesity is a major health problem in the Western world, affecting approximately one third of the adult general population (Flegal et al., 1998; Kopelman, 2000). Obesity is independently associated with increased cardiovascular morbidity and mortality, and cardiac pathology is common. Previous studies have mainly relied on surface echocardiography and have reported higher left ventricular mass and volumes, and abnormal diastolic filling pattern in the obese (Alpert et al., 1995; Alpert et al., 1997; Crisostomo et al., 1999; Kasper et al., 1992; de Simone et al., 1994). However, echocardiography is often suboptimal for evaluation of the obese due to limited acoustic penetration (Chuang et al., 2001; Gottdiener et al., 1995; Schirmer et al., 1999) and geometric assumptions used to estimate global indexes. Therefore, quantitative echocardiographic assessment of left and particularly right ventricular volumes and ejection fraction is subject to considerable measurement error.

Cardiovascular magnetic resonance imaging (CMR) offers several advantages for evaluation of cardiac structure and function in the obese. The high accuracy and reproducibility of the technique allows for detection of very small changes in left ventricular indexes with a relatively small sample size, as compared with echocardiography (Bellenger et al., 2000). Besides global indexes of cardiac anatomy and function, such as ventricular volumes, mass, ejection fraction, and cardiac output, CMR can also be used to quantify indexes of cardiac rotation. Myocardial tagging by complementary spatial modulation of magnetization (Stuber et al., 1999a) provides cardiac rotational indexes that can differentiate subjects with left ventricular hypertrophy due to endurance training and aortic stenosis (Stuber et al., 1999). Abnormal apical left ventricular rotation pattern correlates with measures of diastolic dysfunction (Stuber, 2002). There have been no previous studies assessing the potential utility of CMR and myocardial tagging in the obese. Accordingly, we exploited these imaging tools to assess cardiac structure and function in a well-defined population of clinically healthy obese men, and compared these data to a group of age-matched, healthy, lean males.

METHODS

The study was approved by the hospital Committee on Clinical Investigation, and written informed consent was obtained from all subjects. After a 10–15 min supine rest period, bilateral arm blood pressure was measured with an automated sphygmomanometer (Dinamap, GE Medical Systems, Milwaukee, WI) using a large cuff for the obese subjects and standard cuff for lean men. The mean of both arm measurements was used for data analysis. The subjects' height and weight were measured, using a wall-mounted stadiometer (Holtain Ltd, Crymych Pembs., United Kingdom) and a 600 lb capacity electronic scale (Model 0501, ACME, San Leandro, CA). The subjects' body mass index, calculated as weight (kg) divided by height (m) squared, and body surface area (Dubois and Dubois, 1916) were recorded. Waist and hip circumference were measured using a nonelastic measuring tape (Callaway et al., 1988) and their ratio was determined. To exclude potential lifestyle differences between study groups that might affect cardiovascular function, we also collected data regarding subjects' habits on exercise (hours per week), coffee (cups per week), and alcohol consumption (servings per week).

Subjects

Fifty healthy men aged 20–40 years, including 25 obese (body mass index $> 30\,kg/m^2$) and 25 lean subjects (body mass index $19–25\,kg/m^2$) were recruited. Exclusion criteria were: 1) known cardiac diseases including congenital, valvular, ischemic or nonischemic cardiomyopathy, and arrhythmias; 2) known hypertension (under dietary or pharmacological treatment), or cuff arm blood pressure at the time of testing of $>160/90$ mmHg; 3) endocrine diseases including diabetes mellitus (under dietary or pharmacological treatment) or fasting venous blood "fingerstick" glucose > 105 mg/dl measured on portable glucometer (OneTouch, LifeScan, Milpitas, CA), or use of any hormones or other medications that affect endocrine function within 2 months of participation; 4) known hepatic or renal dysfunction; 5) previously diagnosed sleep-apnea syndrome, or suggestive symptoms, including ≥ 2 of the following: loud snoring, frequent nocturnal awakening (>3/night period), daytime hypersomnolence, frequent early-morning headaches; 6) recent (<2 weeks) acute illness or injury; 7) recent (<1 month) weight gain or loss of >5 kg; 8) previous or current use of cocaine or intravenous recreational drugs; and 9) contraindications to CMR including severe claustrophobia and metallic implants or devices.

Cardiovascular Magnetic Resonance Imaging

All imaging was performed using a 1.5 T whole body scanner (Philips Gyroscan ACS/NT, Best, The Netherlands) with a 60 cm diameter bore,

Powertrak 6000 gradients (23 mT/m, 219 μsec rise time), and a 5-element cardiac synergy coil.

After initial localizing scans, cine left ventricular long-axis, 4-chamber and contiguous short axis images (slice thickness 10 mm) were obtained as previously described (Salton et al., 2002), using an electrocardiogram-triggered hybrid gradient-echo/echoplanar breath-hold sequence (300–360 mm field-of-view, 128×256 matrix, echoplanar factor of 7 and echo time of 9.1 msec). Temporal resolution was 30–35 msec, and the breath-hold duration was 10–12 sec.

Myocardial tagging was employed to obtain images of the apical left ventricular (short axis orientation) with orthogonally positioned tag lines as previously described (Stuber et al., 1998; Stuber et al., 1999a). The tagged slice was visually positioned 1 cm from the endocardial apical border. Our analysis concentrated on the apical myocardium, as the rotational characteristics of this region have been previously shown to better represent the rotational pattern of the entire ventricle (Stuber et al., 1999b). The temporal resolution of the tagged images was 35 msec (Stuber et al., 1998; Stuber et al., 1999a).

Data Analysis

Left and right ventricular endocardial and epicardial contours for end-diastolic and end-systolic short axis images were manually traced on a commercial analysis workstation (EasyVision 4, Philips Medical Systems, Best, The Netherlands). To minimize interobserver variability, all tracing was performed by a single experienced observer, blinded to patient data. Using a commercially available analysis package (EasyVision 4), volumetric assessment of mass, end-diastolic and end-systolic volumes, ejection fraction, stroke volume, and cardiac output were derived for each ventricle, as previously described (Lorenz et al., 1999 Marcus et al., 1999;). To obtain data comparable to those reported by echocardiography, we measured the wall thickness-to-cavity radius ratio from the short axis images at the basal one-third of the left ventricular cavity (7 cm from the apex). The ratio of left ventricular mass to end-diastolic volume (a three-dimensional measure of the left ventricular geometry) was also calculated.

Complementary spatial modulation of magnetization (CSPAMM) tagging data were analyzed on a Linux workstation by a single experienced observer, using a semiautomated custom-written software operating on PV-Wave platform (PV-Wave Extreme Advantage, Research Systems, Inc., Boulder, Co, USA) (Stuber et al., 1998). Among tagging indexes, we selected the local myocardial rotation, its first derivative (the rotational velocity), the maximal systolic (counter-clockwise) and diastolic (clockwise) rotational velocities and the time-delay to these values, as these parameters have been previously shown to differentiate the "physiological" exercise-induced left ventricular hypertrophy of endurance athletes from the "pathological" hypertrophy caused by severe aortic stenosis (Stuber et al., 1999b). Myocardial tagging data were all referenced to end systole and expressed as percent of end systole.

Statistical Analysis

All data are presented as mean ± one standard deviation. Baseline population characteristics on weekly exercise and consumption of alcohol and coffee were compared using the Mann-Whitney U test. For continuous variables, comparisons between groups were performed using the Student's t-test. Both absolute values for left and right ventricular parameters and height-indexed values were compared between groups. Because various height-based methods for indexing left ventricular mass in the obese have been proposed (Hense et al., 1998; Lauer et al., 1994; Pankow et al., 2000; Weiss et al., 1996), an additional analysis was performed by indexing left ventricular mass by height$^{(2.7)}$ (Gosse et al., 1999; Hense et al., 1998). Analysis of covariance was used to adjust for possible confounding factors, when appropriate. Repeated measures analysis of variance was performed to compare myocardial tagging data, for which multiple values were obtained through the cardiac cycle for each subject. All statistical comparisons were two-tailed, with $p < 0.05$ considered significant.

RESULTS

The demographic characteristics of the entire study population are presented in Table 1. Due to selection criteria, obese subjects had significantly greater body weight, waist-to-hip ratio, body surface area, and body mass index (all $p < 0.001$). Though in the normal range (as dictated by inclusion criteria), both the heart rate and the systolic blood pressure were higher in the obese group ($p < 0.001$ for both comparisons). There were no lifestyle differences between groups regarding weekly exercise and alcohol or coffee consumption.

All subjects completed the CMR examination without complications. Though not formally recorded, imaging time for cardiac structure and function was generally <45 minutes. Due to time constraints,

Table 1. Demographic characteristics of the study population.

	Lean	Obese	p value
Age (years)	29 ± 5	30 ± 7	NS
Height (m)	1.76 ± 0.07	1.79 ± 0.07	NS
Weight (kg)	70.4 ± 5.9	111.2 ± 12.8	<0.001
Waist-to-hip ratio	0.85 ± 0.04	0.96 ± 0.07	<0.001
Body mass index (kg/m^2)	22.7 ± 1.7	34.8 ± 2.9	<0.001
Body surface area (m^2)	1.86 ± 0.11	2.28 ± 0.17	<0.001
Exercise (hours/week)	3.7 ± 3.4	3.5 ± 3.6	NS
Coffee (cups/week)	5.1 ± 6.5	3.9 ± 6.1	NS
Alcohol (servings/week)	2.2 ± 1.6	1.8 ± 2.2	NS
Heart rate (min^{-1})	59 ± 7	67 ± 11	<0.001
Systolic blood pressure (mmHg)	121 ± 11	132 ± 11	<0.001
Diastolic blood pressure (mmHg)	73 ± 7	75 ± 8	NS

Abbreviations: NS = nonsignificant.

myocardial tagging data were not obtained in two obese and one lean individuals. Image quality was not formally evaluated, and, though in general images were better for the lean subjects, all images were adequate for evaluation.

Left Ventricular Indexes

Anatomic and functional left ventricular indexes are summarized in Table 2. The obese had greater absolute left ventricular end-diastolic volume ($p < 0.05$), mass ($p < 0.001$), cardiac output ($p < 0.001$), wall thickness-to-cavity radius ratio ($p < 0.05$), and mass to end-diastolic volume ratio ($p < 0.05$), compared to lean controls. The increase in left ventricular mass persisted after covariate adjustment for systolic blood pressure ($p < 0.005$). There were no significant differences in left ventricular end-systolic volume or ejection fraction between obese and lean groups. Differences in left ventricular end-diastolic volume and mass remained significant when indexed for height ($p < 0.05$ and $p < 0.001$, respectively), but not for body surface area (data not shown). For left ventricular mass indexation to height$^{(2.7)}$, the difference between obese and lean remained significant ($p < 0.001$).

Right Ventricular Indexes

Anatomical and functional right ventricular indexes are summarized in Table 3. The obese had

Table 2. Anatomical and functional left ventricular indexes in lean and obese groups.

	Lean	Obese	p value
LV end-diastolic volume (mL)	156 ± 25	176 ± 29	<0.05
LV end-diastolic volume/height (mL/m)	88 ± 13	98 ± 15	<0.05
LV end-systolic volume (mL)	47 ± 11	50 ± 14	NS
LV stroke volume (mL)	109 ± 18	125 ± 20	<0.005
LV ejection fraction (%)	70 ± 5	72 ± 6	NS
LV mass (g)	163 ± 22	203 ± 38	<0.001
LV mass/height (g/m)	93 ± 12	113 ± 17	<0.001
LV mass/height$^{2.7}$ (g/m$^{2.7}$)	36 ± 5	42 ± 5	<0.001
LV wall thickness-to-cavity radius ratio	0.35 ± 0.03	0.39 ± 0.08	<0.05
LV mass / end-diastolic volume (g/mL)	1.06 ± 0.14	1.17 ± 0.22	<0.05
Cardiac output (L/min)	6.4 ± 1.3	8.2 ± 1.2	<0.001
Cardiac index (L/min/m^2)	3.5 ± 0.7	3.6 ± 0.5	NS

Abbreviation: LV = left ventricular.

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Table 3. Anatomical and functional right ventricular indexes in lean and obese groups.

	Lean	Obese	p value
RV end-diastolic volume (mL)	155 ± 28	179 ± 36	<0.05
RV end-diastolic volume / height (mL/m)	88 ± 14	96 ± 27	NS
RV end-systolic volume (mL)	57 ± 21	65 ± 27	NS
RV stroke volume (mL)	94 ± 26	113 ± 22	<0.01
RV ejection fraction (%)	63 ± 10	64 ± 10	NS
RV mass (g)	87 ± 18	105 ± 25	<0.01
RV mass/height (g/m)	50 ± 10	56 ± 17	NS
RV mass/height$^{2.7}$ (g/m$^{2.7}$)	19 ± 4	21 ± 6	NS

Abbreviation: RV = right ventricular.

increased absolute right ventricular end-diastolic volume ($p < 0.05$) and mass ($p < 0.005$) compared to the lean controls, but there were no significant differences in end-systolic volume or ejection fraction. The difference in right ventricular mass between groups did not persist after indexing for height or height$^{2.7}$ [p = NS (non-significant) for both comparisons].

Apical Left Ventricular Rotation

The apical left ventricular rotation throughout the cardiac cycle (Fig. 1) was similar in the obese and the lean ($p = 0.1$). However, in early diastole (110–140% of end systole) there was higher apical left ventricular rotation in the obese ($p < 0.05$). The means of the individual maximal values of apical systolic rotation (which is higher than the peaks of the curves in Fig. 1, as the maximal rotation did not occur at the same time relative to end systole in all subjects) were similar in the obese (11.3 ± 3.6°) and the lean (10.2 ± 2.5°, $p = 0.2$). There was a trend for maximal rotation to occur later in the cardiac cycle for the obese (88 ± 9 vs. 81 ± 13% of end systole, $p = 0.073$).

The rotational velocity pattern of the apical left ventricle (Fig. 2) was significantly different between obese and lean individuals ($p < 0.001$). Though the series data differed significantly, the average peak systolic velocity (counterclockwise rotation) of the obese (64 ± 26°/sec) was similar to that of the lean (60 ± 13°/sec, $p = 0.5$), and occurred at similar time points in the two groups (25 ± 15 vs. 30 ± 16% of end systole, $p = 0.3$). Similarly, the average peak diastolic velocity (clockwise rotation) was similar between the obese and

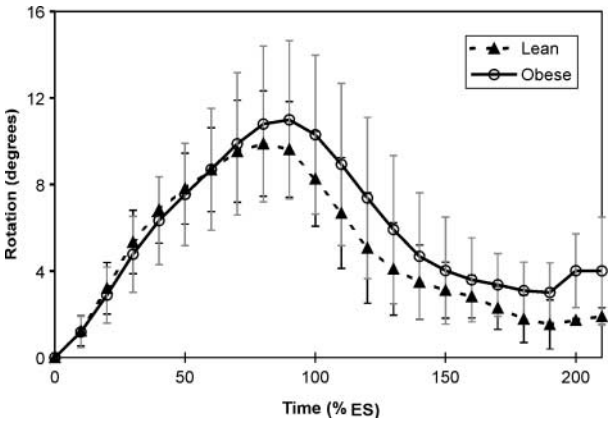

Figure 1. Rotation of the apical left ventricular throughout the cardiac cycle, expressed as percent of end systole (% ES). The curves represent the mean values of the obese and lean groups for each time point and are different ($p = 0.03$) for the early diastolic period (110–140% of end systole).

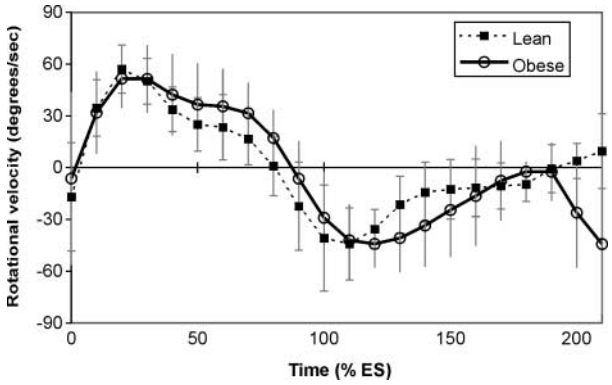

Figure 2. Rotational velocity of the apical left ventricular throughout the cardiac cycle, expressed as percent of end systole (% ES). Rotation occurs in a counterclockwise direction (positive velocity values) during ventricular systole, and clockwise (negative velocity values) during late systole and diastole. The curves represent the mean values of obese and lean individuals for each time point and are significantly different ($p < 0.001$) between the two groups.

the lean (62 ± 26 vs. $57 \pm 20^{\circ}/\text{sec}$, $p = 0.5$), and tended to occur later in the obese (120 ± 36 vs. $102 \pm 33\%$ of endsystole, $p = 0.088$).

DISCUSSION

In this prospective cross-sectional study we used CMR to characterize the cardiac structure and function of clinically healthy adult obese men and demonstrate an increase in absolute left and right ventricular myocardial mass and end-diastolic volumes. The absolute cardiac output was also higher, and subtle abnormalities of apical cardiac rotation could be detected in the obese as compared to lean controls. To our knowledge, this is the first CMR study to focus on the obese and highlights the potential advantages of this technology in a broad population that is often difficult to assess using more conventional noninvasive imaging modalities.

Our study confirms findings from previous echocardiographic studies, which in selected populations have also reported left ventricular hypertrophy with obesity (Alpert et al., 1995; Crisostomo et al., 1999). Our data suggest that in the obese there is cardiac remodeling with increased left ventricular mass and end-diastolic volume, and associated increased wall thickness-to-cavity radius ratio and mass-to-end-diastolic volume ratio. The most appropriate way to normalize left ventricular mass for anthropometric measures has been debated, and indexing for height or a power of height has been suggested to be more appropriate for the obese Gosse et al., 1999; Hense et al., 1998; Lauer et al., 1994; Pankow et al., 2000; Weiss et al., 1996)). In our study differences in left ventricular mass between lean and obese groups persisted for all height-based indexations.

Though we specifically excluded hypertensive subjects and those with known or probable sleep apnea (a well-known predisposing factor for hypertension in the obese (Pankow et al., 2000; Weiss et al., 1996)), systolic blood pressure was still higher in the obese group. Without excluding subjects with sleep apnea, previous studies have also shown that even within the normal range, the obese tend to have higher blood pressures than age- and gender-matched lean individuals (Pozzan et al., 1997; de Simone et al., 1994). The differences in left ventricular mass between obese and lean groups remained after adjusting for systolic blood pressure, demonstrating that obesity is an independent predisposing factor for left ventricular hypertrophy. This is consistent with prior echocardiography data (Gottdiener et al., 1995; Lauer et al., 1992; de Simone et al., 1994). Previous reports have also associated left ventricular mass with a variety of anatomical and functional cardiac parameters (Chen et al., 1998).

A unique finding of our study is the identification of an increase in the absolute right ventricular mass and end-diastolic volume in the obese. Previous investigators have reported similar findings only for obese individuals with sleep apnea and/or pulmonary hypertension (Berman et al., 1991; Noda et al., 1995), subjects we specifically sought to exclude. The reason for this apparent discrepancy is likely the increased accuracy of CMR, particularly in the obese (Chuang et al., 2001). In our analysis, the right ventricular stroke volume was slightly higher than the left ventricular one. This is likely due to the prominent right ventricular trabeculations. Right ventricular trabeculations were considered as "cavity" in the end diastolic image, as they appear separate from the right ventricular free wall. In contrast, trabeculations become indistinguishable from the right ventricular free wall in the end-systolic image and are considered as one structure. This likely accounts for slightly greater apparent right ventricular stroke volume, in both the lean and the obese. Thus, the systematic overestimation of right ventricular stroke volume is unlikely to affect intergroup differences.

Left and right ventricular ejection fractions were similar among the obese and lean groups. However, due to larger end-diastolic volume and higher heart rate, both absolute stroke volume and forward cardiac output were higher in the obese. This increase in cardiac output likely represents an adaptive mechanism, to supply adequate perfusion to an increased tissue mass.

Our methodology for assessment of cardiac rotation has the advantage of visualizing the tag lines late into the cardiac cycle, allowing for evaluation of diastolic cardiac function. Diastolic abnormalities in the obese appear to precede systolic dysfunction, as suggested by the subtle structural changes and apical ventricular rotation abnormalities found in our study, with normal systolic function. However, myocardial tagging only partially assesses diastolic function, and our technique cannot provide stress–strain analyses reported by other myocardial tagging approaches (Azhari et al., 1993; Buchalter et al., 1990). Furthermore, the long analysis time (approximately 2 hours per subject) makes this analysis impractical for clinical use at the present time.

The clinical implication of the difference in systolic and diastolic rotation patterns between obese and lean individuals is uncertain. While the global pattern of apical left ventricular rotation was different between obese and lean groups, peak rotational indices were similar between the two groups. The timing of maximal systolic rotation appeared to best differentiate the obese

and lean groups. However, our study was underpowered to detect such a difference. For a difference in the occurrence of maximal apical torsion of 7% of end systole (equal to the difference found in our study), with an average standard deviation of 10% of end systole (the measured standard deviation in our study was 7–13% of end systole), 34 subjects in each group would be needed, assuming 80% power. A similar abnormal pattern of apical cardiac rotation has been previously described in patients with hypertrophy due to aortic stenosis (Stuber et al., 1999b). It is uncertain whether this reflects an adaptation process of the left ventricle to the primary etiology, or whether it is an untoward outcome of pathological hypertrophy.

Our study was cross-sectional and did not address the effect of weight reduction, nor does it explain the etiology of the cardiac abnormalities of obesity. Our study included only men, because the variability of hemodynamic parameters during the menstrual cycle in women (Manhem et al., 1992; Moran et al., 2000) might confound our measurements. A single previous echocardiographic study has suggested that obese women have similar cardiac abnormalities (Crisostomo et al., 1999). Finally, though our study demonstrated that CMR can be safely performed in obese individuals with body mass index up to 40.7 kg/m^2, morbidly obese individuals would not be well suited for CMR due to physical constraints. Until more data are available, our results should not be extrapolated to the morbidly obese.

From our data it remains uncertain as to whether these changes are the beginning of the process leading to the "cardiomyopathy of obesity," an ill-defined entity characterized by depressed systolic function (Kasper et al., 1992), or whether the changes represent an adaptive change to meet the increased hemodynamic requirements posed by the greater body mass, and thus have no further significance. If such a clinical significance and prognostic value were demonstrated in prospective investigations, the high precision, accuracy, and noninvasive nature of CMR would uniquely position this modality for both initial and follow-up cardiovascular evaluation, in this large portion of the general population.

In conclusion, obesity is associated with cardiac remodeling in clinically healthy men, independent of arterial blood pressure or other comorbidities. Cardiovascular magnetic resonance imaging can be applied reliably in the obese and detect subtle cardiac abnormalities, and may thus be the preferred imaging technique to evaluate cardiac structure and function in these individuals.

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