Obese Subjects Show Sex-Specific Differences in Right Ventricular Hypertrophy

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Background—As right ventricular (RV) remodeling in obesity remains underinvestigated, and the impact of left ventricular (LV) diastolic dysfunction on RV hypertrophy is unknown, we aimed to investigate whether (1) sex-specific patterns of RV remodeling exist in obesity and (2) LV diastolic dysfunction in obesity is related to RV hypertrophy.

Methods and Results—Seven hundred thirty-nine subjects (women, n=345; men, n=394) without identifiable cardiovascular mortality.4 Therefore, RV remodeling in response to obesity could contribute to the observed obesity-related cardiovascular mortality.

One of the potential reasons for the underinvestigation of RV remodeling in obesity lies in the fact that accurate 2-dimensional echocardiographic assessment of RV size and function is inherently more difficult as a result of the complexity of the shape of the RV, which, in contrast to the ellipsoidal shape of the LV, seems triangular, when viewed from the side, and crescentic, when viewed from above. This is hampered further by the increased difficulty of generating adequate acoustic windows in obesity. Despite these limitations, the majority of these studies have shown RV hypertrophy in obesity.5–8

A few previous studies investigating RV geometry in obesity, have, in the main, not excluded subjects with obesity-related comorbidities, such as hypertension,9 which are known to have independent effects on RV mass.5 In contrast to echocardiography, cardiovascular magnetic resonance imaging is

Key Words: diastole □ hypertrophy, right ventricular □ obesity □ sex

There is now a large body of evidence, suggesting that obesity is linked to heart failure and elevated cardiovascular mortality.1 Research into potential mechanisms behind this has almost entirely focused on changes in the left ventricular (LV) morphology, function, and mortality and has largely ignored the potential role of right ventricular (RV) remodeling. It has recently been shown that RV function is a prognostic marker in chronic heart failure, correlating with symptoms, hospital admission rate, and mortality.2,3 and also that RV hypertrophy is an independent predictor of heart failure and cardiovascular death.4 Therefore, RV remodeling in response to obesity could contribute to the observed obesity-related cardiovascular mortality.

Conclusions—A sex difference in RV remodeling exists in obesity. Whereas men exhibit concentric RV remodeling, women exhibit a mixed pattern of eccentric and concentric remodeling. Regardless of sex, reduced LV diastolic function is associated with concentric RV remodeling. (Circ Cardiovasc Imaging. 2015;8:e002454. DOI: 10.1161/CIRCIMAGING.114.002454.)

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ideally suited to investigate RV geometry in obesity because it is not hampered by the need for acoustic windows and can accurately integrate RV size and function regardless of its shape or the degree of chest wall fat.10

The reasons for the development of RV hypertrophy in obesity, without comorbidities, such as obstructive sleep apnoea or systemic arterial hypertension, have not been explored. In the setting of systemic arterial hypertension, RV hypertrophy is commonplace,11 and it has been attributed to LV diastolic dysfunction and associated pulmonary venous hypertension. It is proposed that this results in increased RV pressure and compensatory RV hypertrophy.12–14 Given the fact that it is well-established that obesity is linked to LV diastolic dysfunction,8,15,16 we hypothesized that a similar mechanism of ventricular interactions occurs in obesity.

Although sex-specific patterns of LV remodeling have been shown in obesity,17,18 whether sex differences in RV remodeling exist in obesity is currently unknown. However, given the sex difference in mortality in obesity1 and the evidence that RV hypertrophy is associated with increased mortality, a sex difference in the pattern of RV hypertrophy could contribute to the sex difference in mortality in obesity.

As a result, the aim of this study was to use cardiovascular magnetic resonance (1) to investigate the effects of obesity, without comorbidities, on RV geometry and function, (2) to determine whether there are sex differences in RV adaptation to obesity, and (3) to investigate whether LV diastolic function is related to RV hypertrophy in obesity.

Methods

Seven hundred thirty-nine subjects (women, n=345; body mass index [BMI] range, 15.3–59.2 kg/m2) without identifiable cardiovascular risk factors were recruited for studies within the University Oxford Centre for Clinical Magnetic Resonance Research. All subjects underwent cardiovascular magnetic resonance to measure LV and RV morphologies and functions. The study was approved by the local research ethics committee, and informed written consent was obtained from each patient.

Inclusion Criteria

All subjects were screened for the presence of identifiable cardiac risk factors and excluded if they had a history of cardiovascular disease, hypertension, diabetes mellitus, smoking, and use of prescription medications, and also if they were pregnant or aged <18 years, or had a history of obstructive sleep apnoea (obese only, by medical interview). All subjects were normotensive at the time of scanning (average of 3 supine measures >10 minutes, <140/90 mm Hg; DINAMAP-1846-SX, Critikon Corp).

Anthropometric Data

Fasting blood tests for glucose and cholesterol were taken on the day of the scanning and analyzed as previously described.19 In addition to BMI, fat mass and waist:hip ratio were evaluated as secondary measures of adiposity. Bio-electric impedance was used to determine the total body fat mass using a Bodystat © 1500 analyser. For the calculation of the waist:hip ratio, the average of 3 waist measurements was recorded (1) at the level of the umbilicus and (2) at the level of the greater trochanter of the femur.

RV and LV Imaging

All imaging was cardiac-gated with a precordial 3-lead electrocardiogram and acquired during the end-expiration breathhold. Steady-state free precession cine sequences were used to acquire localization images followed by optimized LV horizontal and vertical long-axis cines. These were used to acquire a steady-state free precession short-axis stack aligned to the LV to obtain coverage of the entire LV and RV (echo time, 1.5 ms; a repetition time of 3.0 ms; temporal resolution, 47.84 ms; slice thickness, 7 mm; interslice gap, 3 mm; and flip angle of 60°), as previously described.20–22 RV concentric hypertrophy/remodeling was defined in this study as an increase in RV mass accompanied by an increase in the RV mass:volume ratio, whereas RV eccentric hypertrophy/remodeling was defined as an increase in RV mass without change or decrease in the RV mass:volume ratio.

LV Diastolic Function Analysis

Analysis for LV volumes was performed using cmr42 © imaging analysis software. LV short-axis images were manually contoured from the base to apex, and across the cardiac cycle to generate volume–time curves. All diastolic peak filling rate measurements (mL/s) were normalized to EDV (EDV/s), as previously described.20–22 On reproducibility analysis, there was good interobserver (8%) and intraobserver (6%) variability in the peak filling rate measurement.

Statistical Analysis

All statistics were analyzed using SPSS 20 (Chicago, IL) and STATA (StataCorp, Houston, TX). All data were subjected to Kolmogorov–Smirnov tests to establish normal distribution of the data. All presented data were normally distributed and are presented as the mean±SD. To compare sex differences in BMI group data, 2-way-ANOVA analysis with Bonferroni correction and saturated linear regression with robust hc3 standard errors to address the differences in error variance was performed.

Linear regression analysis was used to assess the effect of BMI on RV mass, EDV, stroke volume, RV ejection fraction (RVEF), and RV mass/volume ratio (RVM/VR). We assessed sex differences in the effects of BMI and other predictors using interaction terms in the linear regression models for each outcome. Linearity was assessed by the addition of a quadratic term to the regression analyses. No violations of linearity were observed. The normality of distribution of the standardized errors was assessed, and all standardized errors were normally distributed for the primary associations of interest. The values of P<0.05 were considered as statistically significant.

Results

Anthropomorphic Data

Subjects were separated into groups according to sex and World Health Organization BMI categories. Groups were well-matched for age, BMI, and blood pressure. In addition, all subjects were normotensive, normoglycaemic, and normocholesterolaemic on the day of scanning (Table 1).

RV Function and Obesity

Normal and overweight weight women showed higher RVEF than their male counterparts (normal weight, +2.2%; overweight, +4%; P<0.01 for both analyses). Obese men and women had similar RVEF (Table 1). Of note, there was a positive correlation between BMI and RVEF in men (R=0.18; P<0.001), but not in women (R=0.05; P=0.37), a pattern that
was also seen with total fat mass (men, \( R=0.23; P=0.011 \) and women, \( R=0.025; P=0.75 \)). Interestingly, there was also a weak positive relationship between the waist:hip ratio and RVEF in men and women (men, \( R=0.20 \); women, \( R=0.14 \); both \( P<0.04 \)).

**Sex Differences in RV Morphology**

**RV Mass**

When comparing the regression coefficient for the effect of BMI on RV mass between men and women, women showed a greater RV hypertrophic response to increasing BMI (female RV mass increase, +1.0 g per BMI point increase versus male, +0.8 g per BMI point increase; \( P=0.02 \)).

To assess whether this difference was driven by the difference in regression coefficient for the effect of fat mass on RV mass (Table 2), a second regression model, including a sex fat mass interaction term, was performed. This showed that when fat mass was included in the model, the sex difference in regression coefficient for the effect of BMI on RV mass became nonsignificant (\( P=0.08 \)). Overall, this would suggest that the observed sex difference in BMI on RV mass may be because of a differential effect of fat mass on RV modelling.

**RV End-Diastolic Volume**

In contrast to women, where RV cavity size increased with increasing BMI (+1.0 mL per BMI point increase; \( P<0.001 \); Table 1; Figure 1D), in men, there was no relationship between RV end-diastolic cavity size and increasing BMI (+0.2 mL per BMI point increase; \( P=0.51 \); Figure 1C). Because a sex difference in regression coefficient for the effect of fat mass on RVEDV was observed (Table 2), this was included as an interaction term in repeat regression analysis. This showed that the sex difference in the effect of increasing BMI on RVEDV remained (\( P<0.001 \)).

**RV Mass: Volume Ratio**

Both men and women exhibited an increase in RVM/VR with increasing BMI. On comparing the regression coefficients, the effect of BMI on concentric hypertrophy was equal in men and women (men, +0.004 RVM/VR increase per BMI point increase versus women, +0.005 RVM/VR increase per BMI point increase; \( P=0.47 \); Figure 1E and 1F). RVM/VR was also positively correlated with the secondary measures of adiposity (fat mass: men, \( R=0.47 \) and women, \( R=0.61 \); waist:hip ratio: men, \( R=0.30 \) and women, \( R=0.24 \); all \( P<0.001 \)), but no sex difference in the regression coefficients was observed. A weak positive correlation between total cholesterol and RVM/VR was also seen in women (\( R=0.15 \); \( P=0.014 \)). Overall, this suggests that although cavity dilatation occurs along with elevated RV mass in female obesity (ie, eccentric hypertrophy), a degree of concentric hypertrophy is still present and manifest as increased RVM/VR.

**RV Changes Independent of LV Changes**

To investigate whether RV changes occur independently from LV changes or reflect a response to a general process in obesity, all RV measures were adjusted for the appropriate LV parameter.

When adjusted for LV-EDV, the relationship between BMI and RVEDV did not remain significant in women (\( R=-0.03 ; P=0.59 \)). This suggests that the processes causing RV cavity dilatation are similar to those causing LV cavity dilatation. In contrast, when adjusted for LV mass, RV
mass remained positively correlated with BMI in women ($R=0.31; P<0.001$), but not in men ($R=0.05; P=0.40$), suggesting that the effects of obesity on RV hypertrophy in women occur in response to a mechanism independent from that affecting the LV.

### LV Diastolic Function and RV Mass

Across both sexes, the LV peak diastolic filling rate was negatively correlated to both increasing BMI (Figure 2A and 2B) and increasing LV mass (Figure 2C and 2D). In addition, the LV diastolic peak filling rate was also negatively correlated with RV mass in both men and women (Figure 2E and 2F). Of note, the magnitude of the relationship between the LV peak filling rate and RV mass was similar in women and men (men, +4.6 g RV mass increase per LVEDV/s decrease; women, +4.5 g RV mass increase per LVEDV/s decrease, both $P<0.001$). Furthermore, because the relationship between RV remodeling and BMI persists after adjusting for the LV filling rate (men, $R=0.36$; women, $R=0.56$; both $P<0.001$), this suggests that both obesity and LV diastolic function are related to RV hypertrophy.

### Comparing the Sex-Specific Effects of Obesity on RV and LV Mass

To determine whether obesity has equal effects on RV and LV mass, the relative contribution of RV mass (in percentage terms) to total ventricular mass (combined RV/LV mass) was calculated. As expected, total ventricular mass was moderately/strongly correlated with BMI (Figure 3A and 3B). Whereas there was no relationship between percentage contribution of RV mass to total mass and BMI in men ($R=0.05; P=0.38$), suggesting an equal contribution of LV and RV mass to increased total ventricular mass (Figure 3C), there was a positive relationship between percentage contribution of RV mass to total mass and BMI in women ($R=0.69; P<0.001$), suggesting an equal contribution of LV and RV mass to increased total ventricular mass (Figure 3C). There was a positive relationship between percentage contribution of RV mass to total mass and BMI in men ($R=0.05; P=0.38$), suggesting an equal contribution of LV and RV mass to increased total ventricular mass (Figure 3C). This suggests a disproportionate RV mass increase in women. Given the fact that the relationship between total body fat mass and RV mass is steeper in women than in men (men, +0.38 g increase in RV mass [g] per kg increase in total body fat versus women, +0.48 g increase in RV mass [g] per kg increase in total body fat; $P=0.04$), this would suggest that in addition to the effects of LV diastolic dysfunction, the RV in women is more prone to the effects of increased body fat mass.
Relative Effect Size of Diastolic Function and Obesity on RV Hypertrophy

A single BMI point increase overall was linked to a 0.8 g increase in RV mass in men and 1.0 g in women, whereas a single BMI point increase was linked to a 0.07 decrease in LVEDV/s in both men and women (Figure 2). Assuming a linear system, a 0.07 decrease in LVEDV/s would be expected to be associated with a +0.3 g increase in female and male RV mass. Given the overall +0.8 and +1.0 g RV mass increase per BMI point increase, this suggests that only ≈30% to 38% of RV hypertrophy results from LV diastolic dysfunction. In keeping with this, even when adjusted for the effects of LVEDV/s, the positive relationship between BMI and RV mass remained present, although the coefficient of regressions was reduced (men, 0.6 g; women 0.9 g; both P<0.001).

Discussion

It is now well-established that the obesity per se is linked to increased heart failure and cardiovascular mortality. Potential mechanisms for this have focused on the LV, including concentric hypertrophy, diastolic dysfunction, impaired myocardial energetics, and increased aortic stiffness, all of which are present in obesity and are independent markers of elevated cardiovascular risk. Although relatively underinvestigated, RV
hypertrophy is also present in obesity\textsuperscript{9,10} and is emerging as another risk factor for heart failure and cardiovascular death.\textsuperscript{4} This study has shown that even in the absence of traditional cardiovascular risk factors, not only obesity per se is linked to RV hypertrophy (providing another plausible mechanism behind obesity-related mortality) but also sex-specific effects of obesity exist, with concentric RV hypertrophy in men, and mixed eccentric and concentric hypertrophy in women. In addition, with increasing BMI, RV hypertrophy is proportionally greater than LV hypertrophy in women, but equal in men. Furthermore, irrespective of sex, this study has shown that RV hypertrophy is correlated with LV diastolic dysfunction in both men and women.

**Sex Differences in RV Hypertrophy in Response to Increasing BMI**

Although RV hypertrophy has not been widely studied in obesity, previous studies have reported an increase in RV mass with increasing BMI on a population basis, albeit not accounting for comorbidities.\textsuperscript{6,9} In addition, recent echocardiogram-based
studies have highlighted sex-specific RV remodeling with women being more susceptible to RV hypertrophy and diastolic dysfunction in the metabolic syndrome. The Multi-Ethnic Study of Atherosclerosis group, using cardiovascular magnetic resonance, has previously published that obesity is associated with RV hypertrophy without change in ejection fraction. However, as acknowledged by the authors, interpreting the effects of obesity per se in that study is difficult, given the high-prevalence of hypertension, diabetes mellitus, hypercholesterolaemia, and history of smoking and <2% of the Multi-Ethnic Study of Atherosclerosis population were free of cardiovascular risk factors. To date, our work is the only study to investigate the sex-specific effects of increasing BMI, in the absence of comorbidities, on RV geometry. We have shown that although RV hypertrophy is present in both sexes, it is predominantly concentric in men, and mixed eccentric and concentric in women, a difference that may be driven by a sex-specific difference in the effect of fat mass on RV remodeling. Interestingly, this pattern is consistent with findings in the LV, where we have previously reported concentric remodeling in men, and mixed eccentric and concentric remodeling in women.

Independent Effects of Obesity on the RV

Although obesity is well-known to have significant effects on the LV, it is not known that whether coexisting RV hypertrophy occurs in response to the same mechanisms, ie, a generalized cardiac response to increased adiposity, or reflects a response to RV specific stimuli occurring independently of those affecting the LV. In this study, we have shown that RV hypertrophy and cavity dilatation (women only) occur even when adjusted for the appropriate LV characteristics. Possible mechanisms for these effects include adipokines, such as leptin, which have been shown to be linked with rodent cardiomyocyte hypertrophy in vitro and associated with RV hypertrophy in humans. Although it seems logical that greater RV hypertrophy could result from obstructive sleep apnea and chronic pulmonary hypertension, the available published data do not necessarily support this hypothesis. In fact, studies have reported that the majority of obese subjects do not have enough tricuspid valve regurgitation to estimate pulmonary artery pressures, and those that do have generally have normal derived RV systolic pressures.

As this study has shown that women had proportionately greater RV hypertrophy than men in response to increasing BMI and fat mass, independent of the effects on the LV, this suggests that either generalized humoral factors (circulating cytokines, growth hormones, and adipokines), such as angiotensin II, aldosterone, catecholamines, insulin, and leptin, have greater effects on RV myocardial hypertrophy in women or sex-specific factors, for example, sex hormones, are in some way responsible.

Effect of LV Diastolic Function on RV Mass

Another potential mechanism for RV hypertrophy in obesity is LV diastolic dysfunction, which is not only present in obesity but also has been linked to RV hypertrophy in other diseases, such as hypertension. This study has shown that even after adjustment for systolic blood pressure and BMI, the LV peak filling rate is negatively correlated with RV mass. This suggests that as the LV diastolic function worsens, there is an accompanying increase in RV mass. RV hypertrophy in systemic hypertension has been attributed to LV diastolic dysfunction acting via pulmonary venous hypertension and increased RV end-diastolic pressure. Given that obesity is linked to LV diastolic dysfunction, and that this study has shown a negative relationship between LV relaxation and RV mass, it is likely that a similar mechanism is responsible for at least some of the RV hypertrophy seen in obesity. This would then suggest that in addition to the general hypertrophic effects of obesity on the LV and RV, there is an additional RV hypertrophic effect of impaired LV diastolic function.
Comparing the Hypertrophic Effects of Obesity in the RV and LV

This study has shown that, in women, with increasing obesity, RV mass provides a greater contribution to total ventricular mass than LV mass. This pattern is not seen in men. Given the fact that diastolic dysfunction seems to have an equal hypertrophic effect on the RV in men and women, this is unlikely to be the mechanism. One potential explanation may be a differential susceptibility of the RV to metabolic changes. It is now becoming clear that there are sex-specific differences in the effects of the metabolic syndrome risk factors on RV remodeling, with women being more susceptible to RV hypertrophy than men in response to abdominal obesity, impaired fasting glucose, dyslipidemia, and systolic hypertension. In agreement with this, this study has shown a greater effect of obesity on RV hypertrophy in women. Given the steeper relationship between the total body fat mass and RV mass in women, this is likely to be an effect of excess fat, and as a result, changes in adipokines are possible explanations.

RV Morphology and Mortality

It is now becoming recognized that RV hypertrophy is an independent risk factor for both heart failure and cardiovascular mortality. Given the fact that obesity is now unquestionably linked to an increased risk of heart failure, mortality, and RV hypertrophy, it is likely that this is playing a role in the elevated risk associated with increased BMI. This study has shown that increasing BMI, in the absence of identifiable cardiovascular risk factors, and even after adjusting for age, blood pressure, fat mass, and LV size, is associated with RV hypertrophy in both men and women.

Although there is now evidence that cardiovascular magnetic resonance-derived RV mass is predictive of heart failure and death, the effect of the pattern of RV hypertrophy (ie, concentric or eccentric) on mortality is not yet known. However, given the clear differing effects of the various patterns of LV hypertrophy on cardiovascular mortality and morbidity, it is plausible that the same pattern will emerge for the RV. As this study and others have clearly shown the sex-specific effects of obesity, hypertension, and the metabolic syndrome on RV morphology, it is likely that this will turn out to have prognostic importance.

Limitations

The effect of elevated pulmonary pressure on RV morphology is well-established, but it is unknown in this study as invasive pulmonary artery pressure readings were not performed. However, obese participants were excluded if they had a history of obstructive sleep apnoea. In addition, although the prevalence of obstructive sleep apnea on a population basis is greater in men than in women, the relatively greater RV hypertrophy seen in obese women would argue against this being a predominant cause.

Because both blood pressure and cholesterol are both related to RV remodeling and are increased in this study with increasing BMI, they are potential confounders to the results obtained. However, as we have recruited subjects with normal blood pressure and cholesterol levels, observed a small increase in both with increasing BMI (systolic blood pressure, 5–7 mmHg; cholesterol, 0.2–0.5 mmol/L), and have performed adjusted statistical models to account for this, we are confident that the large changes in RV mass observed are related predominantly to obesity and not to changes in blood pressure or cholesterol.

Although RV remodeling patterns have been linked to mortality, this study is not designed or powered to investigate the effects of obesity-related RV remodeling on cardiovascular mortality in this healthy population. Furthermore, large-scale population-based imaging studies, such as, for example, UK Biobank, will be able to address this question.

Conclusions

Although the RV is technically difficult to image, and has traditionally been overlooked, it is becoming increasingly clear that not only is RV hypertrophy linked to a ≥1.9-fold increase in increased mortality over 5 years but also that sex differences in RV remodeling are present in multiple diseases. This study has shown not only that increasing BMI is associated with substantial RV hypertrophy but also the pattern of hypertrophy is different in men, where concentric remodeling occurs, to that seen in women, where mixed eccentric and concentric remodeling occurs. In addition, we have shown that LV diastolic dysfunction is linked to increased RV mass and also that RV hypertrophy in women is relatively greater than LV hypertrophy in obesity. Given the increased risk of heart failure and mortality in obesity, it is likely that RV remodeling is at least, in part, responsible for increased obesity-related mortality, and reducing it may become an important therapeutic target in treating obesity-related heart disease.

Acknowledgments

We thank Bernard Fingleton, PhD (Aberystwyth), MPhil, PhD (Cantab), CStat, AcSS for his help with the statistical analysis.

Sources of Funding

This study was supported by a grant from the Wellcome Trust, British Heart Foundation, and Oxford NIHR Biomedical Research Centre. S. Neubauer and O.R. Rider acknowledge support from the Oxford British Heart Foundation Centre for Research Excellence.

Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

It is becoming increasingly clear that right ventricular (RV) remodeling, and more specifically RV hypertrophy, is linked to increased mortality, and that sex differences in RV remodeling occur in multiple diseases. This study has shown that not only obesity is associated with substantial RV hypertrophy but also a sex-specific difference in remodeling occurs with female obesity being associated with proportionately greater RV hypertrophy. In addition, we have shown that LV diastolic dysfunction in obesity is likely to contribute significantly to RV hypertrophy. Given the increased risk of heart failure and mortality in obesity, it is likely that RV remodeling is at least, in part, responsible for increased obesity-related mortality and reducing it, via weight loss or treatment of diastolic dysfunction may become an important therapeutic target in treating obesity-related heart disease.
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_Circ Cardiovasc Imaging_, 2015;8:
doi: 10.1161/CIRCIMAGING.114.002454
_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

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