

Disclaimer: The manuscript and its contents are confidential,
intended for journal review purposes only, and not to be further
disclosed.

URL: <http://circimaging-submit.aha-journals.org>

Title: Obese Subjects Show Sex-Specific Differences in Right
Ventricular Hypertrophy

Manuscript number: CIRCCVIM/2014/002454R3

Author(s): Oliver Rider, Oxford University

Andrew Lewis, University of Oxford

Adam Lewandowski, University of Oxford

Ntobeko Ntusi, University of Oxford

Mashudu R. Nethononda, Department of Cardiology, Chris Hani

Baragwanath Hospital, University of the Witwatersrand

Steffen Petersen, NIHR Cardiovascular Biomedical Research Unit at

Barts, The London Chest Hospital, Queen Mary, University of London

Jane M. Francis, John Radcliffe Hospital, Oxford, United Kingdom

Alex Pitcher, University of Oxford Centre for Clinical Magnetic

Resonance Research, Oxford, United Kingdom

Rajarshi Banerjee, Oxford Centre for Magnetic Resonance Research

Paul Leeson, University of Oxford

Stefan Neubauer, John Radcliffe Hospital, Oxford, United Kingdom

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.

Obese Subjects Show Sex-Specific Differences in Right Ventricular Hypertrophy

Rider et al: RV Remodeling in Obesity

Oliver J. Rider, BMBCh D.Phil¹; Andrew J.M. Lewis MBBS MRes¹;

Adam J. Lewandowski, BSc, D.Phil²; Ntobeko Ntusi, D.Phil¹; Richard Nethononda, D.Phil¹;

Steffen E. Petersen, MD, DPhil³; Jane M Francis, DCR, DNM¹; Alex Pitcher, BMBCh D.Phil¹;

Rajarshi Banerjee, BMBCh D.Phil¹ Paul Leeson PhD,FRCP²;

Stefan Neubauer MD, FRCP, FACC, FMedSci¹

¹Oxford Centre for Clinical Magnetic Resonance Research, University of Oxford, UK

²Oxford Clinical Cardiovascular Research Facility, University of Oxford, UK

³William Harvey Research Institute, Queen Mary, University of London, UK

From the Radcliffe Department of Medicine, Division of Cardiovascular Medicine and

University of Oxford Centre for Clinical Magnetic Resonance Research, University of Oxford,

Oxford, UK

Correspondence to:

Dr Oliver Rider BA BMBCh MRCP DPhil

Clinical Lecturer

Department of Cardiovascular Medicine

John Radcliffe Hospital

Oxford, OX3 9DU, UK

(Tel) ++441865221869

(Fax) ++441865222077

Email oliver.rider@gmail.com

Journal Subject Codes :Myocardial biology:[104] Structure, Diagnostic testing:[30] CT and

MRI

Abstract

Background—As right ventricular (RV) remodeling in obesity remains under-investigated, and the impact of LV diastolic dysfunction on RV hypertrophy is unknown, we aimed to investigate 1) if sex specific patterns of RV remodeling exist in obesity and 2) whether or not LV diastolic dysfunction in obesity is related to RV hypertrophy.

Methods & Results—739 subjects (females n=345, males n=394) without identifiable cardiovascular risk factors, (BMI 15.3–59.2 kg/m²) underwent cardiovascular magnetic resonance (1.5T) to measure RV mass (g), RV end-diastolic volume (mls, RV-EDV), RV mass/volume ratio (RVM/VR) and LV diastolic peak filling rate (ml/s). All subjects were normotensive (average 119±11 / 73±8 mmHg), normoglycaemic (4.8±0.5mmol/L) and normocholesterolaemic (4.8±0.9mmol/L) at the time of scanning. Across both sexes, there was a moderately strong positive correlation between BMI and RV mass (males+0.8g, females+1.0g per BMI point increase, both p<0.001). Whereas females exhibited RV cavity dilatation (RV-EDV +1.0ml per BMI point increase, p<0.001), BMI was not correlated with RV-EDV in men (R0.04, p=0.51). Concentric RV remodeling was present in both sexes, with RVM/VR being positively correlated to BMI (malesR0.41, femalesR0.51, both p<0.001). Irrespective of sex, LV peak filling rate was negatively correlated with both RV mass (males R -0.43, females R -0.44, both p<0.001) and RVMV/R (males R-0.37, females R-0.35, both p<0.001).

Conclusions—A sex difference in RV remodeling exists in obesity. Whereas males exhibit concentric RV remodeling, females exhibit a mixed pattern of eccentric and concentric remodeling. Regardless of sex, reduced LV diastolic function is associated with concentric RV remodeling.

Key Words: sex, RV hypertrophy, obesity, cardiovascular magnetic resonance imaging, diastole

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 LV morphology, function and mortality and has largely ignored the potential role of 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 and 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.

One of the potential reasons for the under-investigation of RV remodeling in obesity lies in the fact that accurate 2D echocardiographic assessment of RV size and function is inherently more difficult as a result the complexity of the shape of the RV, which, in contrast to the ellipsoidal shape of the LV, appears triangular when viewed from the side and crescentic when viewed from above. This is further hampered 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

The few previous studies investigating RV geometry in obesity, have, in the main not excluded subjects with obesity-related co-morbidities such as hypertension⁹ which are known to have independent effects on RV mass.⁵ In contrast to echocardiography, cardiovascular magnetic resonance (CMR) imaging is ideally suited to investigate RV geometry in obesity as 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 co-morbidities such as obstructive sleep apnoea or systemic arterial hypertension, have not been explored. In the setting of systemic arterial hypertension, RV hypertrophy is commonplace¹¹ and 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 interaction occurs in obesity.

Although sex-specific patterns of LV remodeling have been shown in obesity^{17, 18} whether or not 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 sex difference in mortality in obesity.

As a result, the aim of this study was to use CMR to investigate 1) The effects of obesity, without comorbidities, on RV geometry and function, 2) to determine whether or not there are sex differences in RV adaptation to obesity and 3) to investigate whether or not LV diastolic function is related to RV hypertrophy in obesity.

Methods

739 subjects (females n= 345, BMI range 15.3–59.2 kg/m²) without identifiable cardiovascular risk factors, were recruited to studies within the University Oxford Centre for Clinical Magnetic

Resonance Research (OCMR). All subjects underwent cardiovascular magnetic resonance to measure LV and RV morphology and function. 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, smoking, use of prescription medications, were pregnant or under 18 years of age or had a history of obstructive sleep apnoea (obese only, by medical interview). All subjects were normotensive at the time of scanning (average of three supine measures over ten minutes <140/90mmHg, DINAMAP-1846-SX, Critikon Corp).

Anthropometric data

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

Right and Left Ventricular Imaging

All imaging was cardiac gated with a precordial three lead ECG and acquired during end expiration breathhold. Steady-state free precession cine sequences were used to acquire

localization images followed by optimized left ventricular horizontal and vertical long-axis cines. These were used to acquire a steady-state free precession (SSFP) short-axis stack aligned to the left ventricle to obtain coverage of the entire left and right ventricles (echo time 1.5ms, a repetition time of 3.0ms, temporal resolution 47.84ms, slice thickness 7mm, interslice gap 3mm, flip angle of 60°), as previously described.²⁰⁻²² RV concentric hypertrophy/remodelling was defined in this study as an increase in RV mass accompanied by an increase in RV Mass: Volume ratio, RV eccentric hypertrophy/remodelling was defined as an increase in RV mass without change or decrease in RV Mass: Volume ratio.

Data Analysis

Image analysis for ventricular volumes and mass was performed using cmr42 © (Circle Cardiovascular Imaging Inc, Calgary, Canada) as previously described.¹⁸ Intra-observer coefficient of variation for RV mass with this method is excellent (9% RV-EDV, 12% RV mass in this study), and in keeping with previously reported data from this group.²³

LV Diastolic Function Analysis

Analysis for LV volumes was performed using CMR⁴² © imaging analysis software. LV short axis images were manually contoured from base to apex, and across the cardiac cycle to generate volume-time curves. All diastolic peak filling rate measurements (ml/s) were normalized to end-diastolic volume (EDV/s), as previously described.²⁴ On reproducibility analysis, there was good inter-observer (8%) and intra-observer (6%) variability in the peak filling rate measurement.

Statistical Analysis

All statistics were analysed using SPSS 20 (Chicago, Ill) and STATA (StataCorp, Texas). All data were subjected to Kolmogorov–Smirnov tests to establish normal distribution of the data. All presented data was normally distributed and is presented as the mean \pm standard deviation. To compare sex differences in BMI group data, two 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, SV, RVEF and 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. Normality of distribution of the standardised errors was assessed, all standardised errors were normally distributed for the primary associations of interest. 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 body mass index (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).

Right Ventricular Function and Obesity

Normal and overweight weight females showed higher RVEF than their male counterparts (normal weight + 2.2%, overweight + 4%, $p < 0.01$ for both analyses). Obese males and females had similar RVEF (Table 1). Of note, there was a positive correlation between BMI and RVEF in males ($R\ 0.18$, $p < 0.001$), but not females ($R\ 0.05$, $p = 0.37$), a pattern that was also seen with total Fat Mass (males, $R\ 0.23$, $p = 0.011$, females, $R\ 0.025$, $p = 0.75$). Interestingly, there was also a weak positive relationship between WHR and RVEF in males and females (males; $R\ 0.20$, females $R\ 0.14$, both $p < 0.04$).

Sex Differences in Right Ventricular Morphology

Right Ventricular Mass

When comparing the regression coefficient for the effect of BMI on RV mass between males and females, females showed a greater RV hypertrophic response to increasing BMI (female RV mass increase +1.0g per BMI point increase vs male, +0.8g 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 non-significant ($p = 0.08$). Overall this would suggest that the observed sex difference in BMI on RV mass may be due to a differential effect of fat mass on RV modelling.

RV End-Diastolic Volume

In contrast to females, where RV cavity size increased with increasing BMI (+1.0mls per BMI point increase, $p < 0.001$, Table 1, Figure 1D), in males there was no relationship between RV

end-diastolic cavity size and increasing BMI (+ 0.2mls per BMI point increase, $p = 0.51$, Figure 1C). As a sex difference in regression coefficient for the effect of fat mass on RV-EDV was observed (Table 2), this was included as an interaction term in repeat regression analysis. This showed that, the sex difference in effect of increasing BMI on RV-EDV remained ($p < 0.001$).

RV Mass: Volume Ratio

Both males and females exhibited an increase in RVM/VR with increasing BMI. On comparing the regression coefficients, the effect of BMI on concentric hypertrophy was equal in males and females (males, +0.004 vs females +0.005 RVM/VR increase per BMI point increase, $p = 0.47$, Figure 1 E&F). RVM/VR was also positively correlated with the secondary measures of adiposity (Fat mass; males $R = 0.47$, Females $R = 0.61$, WHR; males $R = 0.30$, Females $R = 0.24$, all $p < 0.001$), but no sex difference in the regression coefficients was observed. A weak positive correlation also was seen between total cholesterol and RVM/VR was also seen in females ($R = 0.15$, $p = 0.014$). Overall, this suggests that, although cavity dilatation occurs along with elevated RV mass in female obesity (i.e. 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 RV-EDV did not remain significant in females ($R = 0.03$, $p = 0.59$). 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 (female 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 are occurring in response to a mechanism independent from that affecting the LV.

LV Diastolic Function and Right Ventricular Mass

Across both sexes, LV peak diastolic filling rate was negatively correlated to both increasing BMI (Figure 2 A & B) and increasing LV mass (Figure 2 C & D). In addition, LV diastolic peak filling rate was also negatively correlated with RV mass in both men and women (Figure 2 E & F). Of note, the magnitude of relationship between LV peak filling rate and RV mass was similar in women and men (male +4.6g, females +4.5g RV mass increase per LVEDV/s decrease, both $p < 0.001$). Importantly, LV peak filling rate was also related to RV concentric remodeling (men +0.025, females +0.024 RV mass: volume ratio increase per LVEDV/s decrease, both analyses $p < 0.001$). This would suggest that not only is LV diastolic function related to RV concentric remodeling, but also that the magnitude of the effect of diastolic dysfunction in causing RV hypertrophy is similar in men and women. Importantly, even when adjusted for BMI and SBP, LV peak filling rate remained negatively correlated with RV mass (male + 2.9g, females +1.5g RV mass increase per LVEDV/s decrease, both $p < 0.001$). Furthermore, as the relationship between RV remodeling and BMI persists after adjusting for LV filling rate (male $r = 0.36$, females $r = 0.56$, 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

In order to determine whether or not 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 &B). Whereas there was no relationship between percentage contribution of RV mass to total mass and BMI in males, ($R = 0.05$, $p = 0.35$) 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 females, ($R = 0.30$, $p < 0.001$, Figure 3D). This suggests a disproportionate RV mass increase in females. Given the fact that the relationship between total body fat mass and RV mass is steeper in females than males (males $+0.38\text{g}$ vs female $+0.48\text{g}$ 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 females is more prone to the effects of increased body fat mass.

Relative Effect Size of Diastolic Function and Obesity on RV Hypertrophy

Whereas a single BMI point increase overall was linked to a 0.8g increase in RV mass in males and 1.0g in females, 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 $+0.3\text{g}$ increase in female and male RV mass. Given the overall $+0.8$ and $+1.0\text{g}$ RV mass increase per BMI point increase; this suggests that only ~30-38% 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 were reduced (male, 0.6g , females 0.9g , both $p < 0.001$).

Discussion

It is now well established that obesity *per se* is linked to increased heart failure and cardiovascular mortality.²⁵ Potential mechanisms for this have focused on the LV including; concentric hypertrophy,¹⁸ diastolic dysfunction,¹⁶ impaired myocardial energetics²⁶ and increased aortic stiffness,²⁷ all of which are present in obesity and are independent markers of elevated cardiovascular risk. Although relatively under-investigated, RV hypertrophy is also present in obesity^{9,10} and is emerging as another risk factor for heart failure and cardiovascular death.⁴ This study has shown that, even in the absence of traditional cardiovascular risk factors, not only is obesity *per se* linked to RV hypertrophy (providing another plausible mechanism behind obesity related mortality), but also that 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 Right Ventricular 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.^{6,9} In addition, recent echocardiogram-based studies have highlighted sex-specific RV remodelling with females being more susceptible to RV hypertrophy and diastolic dysfunction in the metabolic syndrome. The Multi Ethnic Study of Atherosclerosis (MESA) group, using CMR, have previously published that obesity is associated with RV hypertrophy without change in ejection fraction.⁹ 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, hypercholesterolaemia and history of smoking and less than 2% of the MESA 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 males and mixed eccentric and concentric in females, a difference that may be driven by a sex-specific difference in the effect of fat mass on RV remodelling. Interestingly, this pattern is consistent with findings in the LV, where we have previously reported concentric remodeling in males and mixed eccentric and concentric remodeling in females.¹⁸

Independent Effects of Obesity on the Right Ventricle

Although obesity is well known to have significant effects on the LV,^{18,28} it is not known whether coexisting RV hypertrophy occurs in response to the same mechanisms i.e. 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 (female only) occur even when adjusted for the appropriate LV characteristics. Possible mechanisms for these effects include adipokines such as leptin which has been shown to be linked with rodent cardiomyocyte hypertrophy *in vitro*²⁹ and associated with RV hypertrophy in humans.¹⁰ 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^{7,8} 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.⁷

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

The 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 has been linked to RV hypertrophy in other diseases such as hypertension.¹⁴ This study has shown that even after adjustment for SBP and BMI, LV peak filling rate is negatively correlated with RV mass. This suggests that as 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.¹²⁻¹⁴ Given that obesity is linked to LV diastolic dysfunction^{8, 15, 16} 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 left and right ventricle, 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 females, with increasing obesity, RV mass provides a greater contribution to total ventricular mass than LV mass. This pattern is not seen in males. Given the fact that diastolic dysfunction appears 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 females being more susceptible to RV hypertrophy than males in response to abdominal obesity, impaired fasting glucose, dyslipidemia and systolic hypertension.^{5,6} In agreement with this, this study has showed a greater effect of obesity on RV hypertrophy in females. Given the steeper relationship between total body fat mass and RV mass in females, this is likely to be an effect of excess fat, and as a result, changes in adipokines are a possible explanation.

Right Ventricular Morphology and Mortality

It is now becoming recognized that RV hypertrophy is an independent risk factor for both heart failure and cardiovascular mortality.³ Given the fact that obesity is now unquestionably linked to an increased risk of heart failure, mortality²⁵ 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 males and females.

Although there is now evidence that CMR-derived RV mass is predictive of heart failure and death⁴ the effect of the pattern of RV hypertrophy (i.e. 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^{30,31} it is very plausible that the same pattern will emerge for the RV. As this study, and others, have clearly shown sex specific-effects of obesity, hypertension and the metabolic syndrome on RV morphology it is likely this will turn out to have prognostic importance.

Limitations

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

As both blood pressure and cholesterol are both related to RV remodelling and are increased in this study with increasing BMI, they are potential confounders to the results seen. However, as we have recruited subjects with normal blood pressure and cholesterol levels, observed a very small increase in both with increasing BMI (SBP; 5-7mmHg, Cholesterol (0.2-0.5mmol/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. Future, large scale population-based imaging studies such as, for example, UK Biobank³² will be able to address this question.

Conclusion

Although the right ventricle is technically difficult to image, and has traditionally been overlooked, it is becoming increasingly clear that RV remodeling, and more specifically RV hypertrophy, is linked to increased mortality with up to a 1.9 fold increase over five years⁴ and that sex differences in RV remodeling occur in multiple diseases. This study has not only shown that increasing BMI is associated with substantial RV hypertrophy, but also that 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 females is relatively greater than LV hypertrophy in obesity. Given the increased risk of heart failure and mortality in obesity, it is very 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.

Acknowledgements

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

Sources of Funding

The study was supported by a grants from the Wellcome Trust, British Heart Foundation and by the Oxford NIHR Biomedical Research Centre. SN and OR acknowledge support from the Oxford BHF Centre of Research Excellence

Disclosures

None.

References

1. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, Moore SC, Tobias GS, Anton-Culver H, Freeman LB, Beeson WL, Clipp SL, English DR, Folsom AR, Freedman DM, Giles G, Hakansson N, Henderson KD, Hoffman-Bolton J, Hoppin JA, Koenig KL, Lee IM, Linet MS, Park Y, Pocobelli G, Schatzkin A, Sesso HD, Weiderpass E, Willcox BJ, Wolk A, Zeleniuch-Jacquotte A, Willett WC, Thun MJ. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med.* 2010; 363:2211-2219.
2. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part i: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation.* 2008; 117:1436-1448.
3. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part ii: Pathophysiology, clinical importance, and management of right ventricular failure. *Circulation.* 2008; 117:1717-1731.
4. Kawut SM, Barr RG, Lima JA, Praestgaard A, Johnson WC, Chahal H, Ogunyankin KO, Bristow MR, Kizer JR, Tandri H, Bluemke DA. Right ventricular structure is associated with the risk of heart failure and cardiovascular death: The multi-ethnic study of atherosclerosis (mesa)--right ventricle study. *Circulation.* 2012; 126:1681-1688.
5. Tadic MV, Ivanovic BA, Petrovic M. Is gender responsible for everything? The relationship between sex and right ventricular remodeling in metabolic syndrome. *Echocardiogr-J Card.* 2013; 30:778-785.
6. Tadic M, Ivanovic B, Grozdic I. Metabolic syndrome impacts the right ventricle: True or false? *Echocardiography.* 2011; 28:530-538.
7. Wong CY, O'Moore-Sullivan T, Leano R, Hukins C, Jenkins C, Marwick TH. Association of subclinical right ventricular dysfunction with obesity. *J Am Coll Cardiol.* 2006; 47:611-616.
8. Otto ME, Belohlavek M, Khandheria B, Gilman G, Svatikova A, Somers V. Comparison of right and left ventricular function in obese and nonobese men. *Am J Cardiol.* 2004; 93:1569-1572.

9. Chahal H, McClelland RL, Tandri H, Jain A, Turkbey EB, Hundley WG, Barr RG, Kizer J, Lima JAC, Bluemke DA, Kawut SM. Obesity and right ventricular structure and function the mesa-right ventricle study. *Chest*. 2012; 141:388-395.
10. Rider OJ, Petersen SE, Francis JM, Ali MK, Hudsmith LE, Robinson MR, Clarke K, Neubauer S. Ventricular hypertrophy and cavity dilatation in relation to body mass index in women with uncomplicated obesity. *Heart*. 2011; 97:203-208.
11. Nunez BD, Messerli FH, Amodeo C, Garavaglia GE, Schmieder RE, Frohlich ED. Biventricular cardiac hypertrophy in essential hypertension. *Am Heart J*. 1987; 114:813-818.
12. Akintunde AA, Akinwusi PO, Familoni OB, Opadijo OG. Effect of systemic hypertension on right ventricular morphology and function: An echocardiographic study. *Cardiovascular journal of Africa*. 2010; 21:252-256.
13. Cuspidi C, Negri F, Tadic MV, Sala C, Parati G. Left atrial enlargement and right ventricular hypertrophy in essential hypertension. *Blood Press*. 2014; 23:89-95.
14. Raman SV. The hypertensive heart. An integrated understanding informed by imaging. *J Am Coll Cardiol*. 2010; 55:91-96.
15. Peterson LR, Waggoner AD, Schechtman KB, Meyer T, Gropler RJ, Barzilai B, Davila-Roman VG. Alterations in left ventricular structure and function in young healthy obese women: Assessment by echocardiography and tissue doppler imaging. *J Am Coll Cardiol*. 2004; 43:1399-1404.
16. Rider OJ, Francis JM, Ali MK, Petersen SE, Robinson M, Robson MD, Byrne JP, Clarke K, Neubauer S. Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. *J Am Coll Cardiol*. 2009; 54:718-726.
17. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension*. 1994; 23:600-606.
18. Rider OJ, Lewandowski A, Nethononda R, Petersen SE, Francis JM, Pitcher A, Holloway CJ, Dass S, Banerjee R, Byrne JP, Leeson P, Neubauer S. Gender-specific differences in left ventricular remodelling in obesity: Insights from cardiovascular magnetic resonance imaging. *Eur Heart J*. 2013; 34:292-299.
19. Rider OJ, Tayal U, Francis JM, Ali MK, Robinson MR, Byrne JP, Clarke K, Neubauer S. The effect of obesity and weight loss on aortic pulse wave velocity as assessed by magnetic resonance imaging. *Obesity (Silver Spring)*. 2010; 18:2311-2316.
20. Lewandowski AJ, Bradlow WM, Augustine D, Davis EF, Francis J, Singhal A, Lucas A, Neubauer S, McCormick K, Leeson P. Right ventricular systolic dysfunction in young adults born preterm. *Circulation*. 2013; 128:713-720.
21. Lewandowski AJ, Augustine D, Lamata P, Davis EF, Lazdam M, Francis J, McCormick K, Wilkinson AR, Singhal A, Lucas A, Smith NP, Neubauer S, Leeson P. Preterm heart in adult life: Cardiovascular magnetic resonance reveals distinct differences in left ventricular mass, geometry, and function. *Circulation*. 2013; 127:197-206.
22. Rider OJ, Nethononda R, Petersen SE, Francis JM, Byrne JP, Leeson P, Clarke K, Neubauer S. Concentric left ventricular remodeling and aortic stiffness: A comparison of obesity and hypertension. *Int J Cardiol*. 2013; 167:2989-2994.
23. Hudsmith LE, Petersen SE, Francis JM, Robson MD, Neubauer S. Normal human left and right ventricular and left atrial dimensions using steady state free precession magnetic resonance imaging. *J Cardiovasc Magn Reson*. 2005; 7:775-782.

24. Zeidan Z, Erbel R, Barkhausen J, Hunold P, Bartel T, Buck T. Analysis of global systolic and diastolic left ventricular performance using volume-time curves by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr*. 2003; 16:29-37.
25. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002; 347:305-313
26. Rider OJ, Francis JM, Ali MK, Holloway C, Pegg T, Robson MD, Tyler D, Byrne J, Clarke K, Neubauer S. Effects of catecholamine stress on diastolic function and myocardial energetics in obesity. *Circulation*. 2012; 125:1511-1519.
27. Rider OJ, Holloway CJ, Emmanuel Y, Bloch E, Clarke K, Neubauer S. Increasing plasma free fatty acids in healthy subjects induces aortic distensibility changes seen in obesity. *Circ Cardiovasc Imaging*. 2012; 5:367-375.
28. Rider OJ, Francis JM, Ali MK, Byrne J, Clarke K, Neubauer S, Petersen SE. Determinants of left ventricular mass in obesity; a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson*. 2009; 11:9.
29. Rajapurohitam V, Gan XT, Kirshenbaum LA, Karmazyn M. The obesity-associated peptide leptin induces hypertrophy in neonatal rat ventricular myocytes. *Circ Res*. 2003; 93:277-279.
30. Gerds E, Cramariuc D, de Simone G, Wachtell K, Dahlöf B, Devereux RB. Impact of left ventricular geometry on prognosis in hypertensive patients with left ventricular hypertrophy (the life study). *Eur J Echocardiogr*. 2008; 9:809-815.
31. Krumholz HM, Larson M, Levy D. Prognosis of left ventricular geometric patterns in the framingham heart study. *J Am Coll Cardiol*. 1995; 25:879-884.
32. Petersen SE, Matthews PM, Bamberg F, Bluemke DA, Francis JM, Friedrich MG, Leeson P, Nagel E, Plein S, Rademakers FE, Young AA, Garratt S, Peakman T, Sellors J, Collins R, Neubauer S. Imaging in population science: Cardiovascular magnetic resonance in 100,000 participants of uk biobank - rationale, challenges and approaches. *J Cardiovasc Magn Reson*. 2013; 15:46.

Table 1. Anthropometric and RV characteristics for the study group separated into WHO BMI categories, normal weight (BMI <25kg/m²), overweight (25 - 29.9 kg/m²) and obese (> 30 kg/m²).

	Normal Weight Male (n=189)	Normal Weight Female (n=210)	Overweight Male (n=96)	Overweight Female (n=85)	Obese Male (n=60)	Obese Female (n=99)
Age	35 ± 12	35 ± 18	38 ± 13	42 ± 14 [†]	44 ± 13 [‡]	42 ± 11
Body Mass Index (kg/m²)	22 ± 2	22 ± 2	27 ± 1 [#]	27 ± 1	35 ± 6 [‡]	38 ± 7
Systolic Blood Pressure (mmHg)	120 ± 10	115 ± 10	123 ± 8	118 ± 12	125 ± 9 [‡]	122 ± 12 ^{**}
Diastolic Blood Pressure (mmHg)	73 ± 8	71 ± 8	76 ± 7	74 ± 9	77 ± 7 [‡]	76 ± 8 ^{**}
Right Ventricular Ejection Fraction (%)	61 ± 7 [*]	63 ± 8	60 ± 7 ^{††}	65 ± 6	63 ± 8	63 ± 6
Right Ventricular End-Diastolic Volume (mL)	171 ± 30 [*]	128 ± 24	175 ± 30 ^{††}	133 ± 26	167 ± 33 [‡]	144 ± 23 ^{**}
Right Ventricular Mass (g)	41 ± 9 [*]	32 ± 8	47 ± 9 ^{#††}	37 ± 8 [†]	51 ± 11 [‡]	48 ± 12 ^{**}
Right Ventricular Mass/Volume Ratio	0.24 ± 0.05 [*]	0.25 ± 0.06	0.27 ± 0.06 [#]	0.28 ± 0.06 [†]	0.32 ± 0.08 [‡]	0.33 ± 0.08 ^{**}
RV stroke Volume (ml)	104 ± 20	81 ± 17	107 ± 20	87 ± 17	106 ± 21	92 ± 17 ^{**}
Fasting Cholesterol (mmol/L)	4.4 ± 0.8	4.8 ± 0.9	4.9 ± 0.09 [#]	4.8 ± 0.8 [†]	4.9 ± 0.9 [‡]	5.0 ± 0.8
Fasting Glucose (mmol/L)	4.7 ± 0.5	4.7 ± 0.5	5.0 ± 0.5	4.8 ± 0.5	5.0 ± 0.6	5.0 ± 0.5 ^{**}

* p < 0.05 Normal Weight Males versus Normal Weight Females

p < 0.05 Overweight Males versus Normal Weight Males

† p < 0.05 Overweight Females versus Normal Weight Females

‡ p < 0.05 Obese Females versus Obese Males

‡ p < 0.05 Obese Males versus Overweight Males

‡ p < 0.05 Obese Males versus Normal Weight Males

** p < 0.05 Obese Females versus Normal Weight Females

†† p < 0.05 Overweight Females versus overweight Male

Table 2. Gender Differences in Linear Regression for RV Mass, EDV and RVM/VR

<i>RV Mass (g)</i>	<i>Male</i>			<i>Female</i>			<i>Sex Interaction</i>
	R²	β	p value	R²	β	p value	p Value
Body Mass Index (kg/m²)	0.18	0.8	<0.001	0.4	0.1	<0.001	0.009
Age (years)	0.08	0.06	0.14	0.01	0.02	0.61	0.998
Systolic Blood Pressure (mmHg)	0.04	0.22	<0.001	0.04	0.2	<0.001	0.214
Diastolic Blood Pressure (mmHg)	0.01	0.14	0.04	0.03	0.27	<0.001	0.06
Fat Mass (Kg)	0.19	0.38	<0.001	0.47	0.54	<0.001	0.047
Waist : Hip Ratio	0.12	34	<0.001	0.07	33.5	<0.001	0.37
<i>RV-EDV(mls)</i>	R²	β	p value	R²	β	p value	<i>Sex Interaction</i> p Value
Body Mass Index (kg/m²)	0	0.2	0.51	0.08	0.97	<0.001	0.01
Age (yrs)	0.02	-0.38	0.004	0.02	-0.26	0.01	0.09
Systolic Blood Pressure (mmHg)	0.04	0.14	0.43	0.02	0.05	0.66	0.06
Diastolic Blood Pressure (mmHg)	0.03	-0.12	0.58	0.01	-0.09	0.56	0.62
Fat Mass (Kg)	0.002	0.04	0.87	0.16	0.56	<0.001	0.006
Waist : Hip Ratio	0.005	20.13	0.33	0.004	17.1	0.28	0.07
<i>RV Mass/Volume Ratio</i>	R²	β	p value	R²	β	p value	<i>Sex Interaction</i> p Value
Body Mass Index (kg/m²)	0.16	0.005	<0.001	0.26	0.005	<0.001	0.69
Age (yrs)	0.04	0.001	<0.001	0.01	0.001	0.04	0.38
Systolic Blood Pressure (mmHg)	0.03	0.001	0.001	0.05	0.001	<0.001	0.69
Diastolic Blood Pressure (mmHg)	0.02	0.001	0.01	0.05	0.002	<0.001	0.22
Fat Mass (Kg)	0.22	0.002	<0.001	0.37	0.003	<0.001	0.71
Waist : Hip Ratio	0.09	0.19	<0.001	0.06	0.19	<0.001	0.95

Figure Legends

Figure 1. Sex Differences in RV Remodeling in Obesity; RV Mass (panels A&B) EDV (panels C&D), and RVM/VR (panels E&F). 95% confidence boundaries for regression lines are shown.

Figure 2. The sex specific relationship between diastolic function and BMI (panels A&B), LV mass (panels C&D) and RV mass (panels E&F). 95% confidence boundaries for regression lines are shown.

Figure 3. The sex specific differential effect of obesity on total ventricular mass (LV + RV Mass, g) in males (A) and Females (B), and RV hypertrophy, presented as percentage contribution of RV mass to total ventricular mass (males C, females D). 95% confidence boundaries for regression lines are shown.

Disclaimer: The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed.





