

Relation Between Obesity, Metabolic Syndrome, Successful Long-Term Weight Reduction, and Right Ventricular Function

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SUMMARY

This study sought to examine the relationships between right ventricular (RV) function and geometry, morbid obesity with and without the metabolic syndrome, and the effect of long-term weight loss. Obese ($n = 153$, BMI 41.2 ± 8.7 kg/m²) and healthy non-obese control subjects ($n = 38$, BMI 25.5 ± 3.3 kg/m²) of similar age and gender distribution were prospectively studied during the course of a 1-year weight reduction program with echocardiography at baseline and after one year of follow up. Function and geometry of the right heart were evaluated by tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (TDI S'), RV myocardial performance index (TEI), RV end-diastolic (RVEDD) and end-systolic diameter (RVESD), area of the right atrium (RAA), and systolic pulmonary artery pressure (PAP). Whereas parameters of systolic and diastolic LV function were significantly worse in the obese subjects than those in the non-obese subjects (EF 66 ± 6 versus $69 \pm 6\%$, $P = 0.004$; E/E' 7.4 ± 2.5 versus 6.3 ± 2.6 , $P = 0.010$), parameters of RV function (TAPSE 25.6 ± 4.5 versus 25.1 ± 3.5 mm, $P = 0.528$; TDI S' 13.5 ± 2.9 versus 13.8 ± 2.9 mm/second, $P = 0.553$; TEI 0.25 ± 0.13 versus 0.28 ± 0.09 , $P = 0.283$) as well as geometry measurements were comparable between the obese and non-obese participants and also in obese subjects with full blown metabolic syndrome. Additionally, successful weight reduction did not alter the RV parameters. Nevertheless, in the few obese subjects with RV dysfunction ($n = 7$), metabolic syndrome parameters were more pronounced than in obese with normal RV function.

Morbid obesity with and without the metabolic syndrome is accompanied by an impaired LV systolic and diastolic function. In contrast, RV function appears to be less affected by obesity independent of the presence of the metabolic syndrome. (Int Heart J 2016; 57: 441-448)

Key words: Adiposity, Heart failure, Echocardiography

Obesity and the metabolic syndrome are fast-growing disorders in western countries which are associated with variant cardiovascular abnormalities leading to a high risk of cardiovascular morbidity and mortality.¹⁾ The Framingham Heart Study demonstrated a 2-fold higher risk of developing heart failure in obese subjects with a body mass index ≥ 30 kg/m² in comparison to non-obese ones in a large community-based sample.²⁾ Moreover, adiposity was described as an independent risk factor for developing heart failure with a population attributable risk of 8.0% in a large prospective cohort study with a follow-up of 19 years.³⁾

Adiposity results in different subclinical changes in cardiac function.¹⁾ Arterial hypertension, impaired glucose tolerance, dyslipidemia, altered hemodynamics, elevation of neurohumoral and inflammatory markers, prothrombotic state, and obstructive sleep apnea are associated conditions which may

further predispose to heart failure.²⁻⁴⁾

While the influence of obesity on left ventricular (LV) function is understood in more detail, such as the correlation of body mass index (BMI) with increased LV mass, LV wall thickness, and an impaired systolic and diastolic LV function,^{1,5-8)} there is only limited evidence on right ventricular (RV) function. These data are mainly collected from obese subjects with multiple preexisting cardiovascular abnormalities resulting in combined heart failure independent of the extent of adiposity.^{9,10)} Although lifestyle modification and weight reduction are routinely recommended to improve symptoms and to reduce cardiovascular risk in the obese with metabolic disorders and exertional dyspnea, their effects on right ventricular function and physical performance have not been studied before.

Thus, the aim of our study was to analyze the association of morbid obesity with and without the metabolic syndrome

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on right ventricular function compared to healthy control participants, and to assess the effect of a long-term multimodal weight reduction program on echocardiographic right ventricular function parameters.

METHODS

Study population: Subjects were participants of the “Obesity Weight Reduction and Remodeling Study”, a prospective longitudinal study evaluating excessive body fat for its pathogenic potential in terms of cardiometabolic diseases and assessing the effects of a considerable weight reduction on interactions in systems biology.

Obese patients of the general population intending to participate in a weight reduction program were offered enrollment in our research study prior to the start of the program. Patients were eligible for enrollment if they were 18-65 years old, present with a BMI ≥ 30 kg/m² and a constant body weight in the last 3 months, and if they signed a declaration of consent. Exclusion criteria were weight reduction $\geq 10\%$ of body weight in the last 6 months, cancer, pregnancy, therapy with steroids or thyroid hormones, known heart disease, known diabetes mellitus type 1 or 2, known inflammatory bowel, rheumatoid, or systemic diseases, known chronic renal failure, known liver diseases, mental disorders, or addiction to drugs or alcohol. In addition, echocardiographic RV function was determined in 38 non-obese control subjects (BMI < 30 kg/m²) of similar age and gender distribution. The metabolic syndrome was defined according to the NCEP-ATP III guidelines, if at least 3 of the following criteria were fulfilled: abdominal obesity with a waist circumference ≥ 102 cm in males and ≥ 88 cm in females, dyslipidemia with triglyceride levels ≥ 150 mg/dL, HDL-cholesterol levels < 40 mg/dL in males and < 50 mg/dL in females, blood pressure $\geq 130/85$ mmHg or treatment for hypertension and fasting plasma glucose levels ≥ 110 mg/dL or presence of diabetes mellitus type 2.¹¹⁾ The participants were recruited by flyers and advertisements. The study was approved by the local Ethics Committee.

Laboratory analyses: Serum samples were collected after a 12 hour overnight fast and immediately stored at -70°C . The samples had not been thawed before the present measurements. Fasting glucose, insulin, and blood lipids were determined by standard methods in the certified clinical chemistry laboratory of the University Hospital. Insulin resistance was estimated by homeostasis model assessment index (HOMA-IR). The NT-proBNP levels were determined by a standard chemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The GDF-15 concentrations were determined by enzyme-linked immunosorbent assay (Quantikine, R&D Systems Europe, Wiesbaden, Germany).

Echocardiography: Echocardiography was performed at baseline and at the end of the weight reduction program (after one year) using a standard ultrasound system (Philips iE33 Philips Medical Systems, Hamburg, Germany). The LV-EF was measured based on the modified biplane Simpson's method. The following parameters were measured according to previous American Society of Echocardiography (ASE) guidelines:¹²⁾ parasternal long axis diameter, and apical 4-chamber area. Measurements were obtained just before mitral valve opening. Left ventricular mass index (LVM) was calculated by

the Devereux formula indexed to the body surface area. Conventional transmitral flow was measured with pulsed wave Doppler. Early (E) and late atrial (A) transmitral peak flow velocities, their ratio (E/A), and the deceleration time (DT) of the early transmitral flow velocity were measured and 3 consecutive beats were averaged. Pulsed wave tissue Doppler imaging (TDI) was performed at the junction of the lateral mitral annulus, and 3 consecutive beats were averaged. Early diastolic velocities (E' lateral) were recorded. Ratios of E/E' lateral were calculated. All measurements were recorded by two expert echocardiographers.

RV function: RV global function was evaluated by tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (systolic velocity across lateral segment of tricuspid annulus; TDI S'), and the right ventricular myocardial performance index (TEI) which was defined as the ratio of total isovolumic time divided by ejection time ((IVRT + IVCT)/ET) using the pulsed tissue Doppler method. Additionally, RV end-diastolic (RVEDD) and end-systolic diameter (RVESD) quantified in the RV-focused view of apical 4-chamber view, area of the right atrium (RAA) measured in ventricular end-systole when the atrium is the largest, and the tricuspid regurgitant jet velocity for estimation of systolic pulmonary artery pressure (PAP) were assessed. All measurements were performed according to the ASE guidelines for the echocardiographic assessment of the right heart in adults.¹³⁾ RV measurements were performed in 191 subjects (153 obese and 38 non-obese control participants). According to the ASE guidelines, a TAPSE < 16 mm, TDI S' < 10 mm/second, or RV TEI > 0.55 yielded high specificity for RV dysfunction.¹³⁾ To achieve a robust presence of RV dysfunction and to minimize false positives, RV dysfunction was assumed if one of these criteria was fulfilled plus at least one other borderline impairment (ie, TAPSE < 20 mm, TDI S' < 11 mm/second, TEI > 0.45).

Physical performance: Patients performed the 6-minute walk test at study entry and at the end of the program after one year. Patients were instructed to walk from end to end in an enclosed corridor, covering as much ground as they could during 6 minutes. The distance walked was measured using an electronic meter counter.

Weight loss program and definition of successful weight reduction: Details of the weight loss programs have been published earlier.¹⁴⁾ Briefly, for the present investigation, morbidly obese subjects participated either in the standardized multimodal Optifast-52 weight reduction program (Nestlé HealthCare Nutrition GmbH, Germany), provided by the Department of Psychosomatic Medicine at the University of Regensburg, Germany, or in a combined exercise and weight reduction program offered by a local fitness gym. “Successful weight reduction” was defined as weight loss $\geq 10\%$ of baseline weight one year after starting the weight reduction program and “failed weight reduction” as weight loss less than 10%. In the present sample successful weight reduction was achieved in 41%.

Statistical analysis: Statistical analyses were performed with SPSS version 18.0 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics are presented as the mean \pm SD for continuous data and as number and percentages for categorical data. Student's *t*-test and analysis of variance (ANOVA) were used to assess linear trends of parameters for normal and independent data. Skewed data were evaluated by the Mann-Whitney *U* test. With respect to longitudinal studies, the paired *t*-test

Table I. Baseline Characteristics of Non-Obese and Obese Study Participants

BMI (kg/m ²)	Non-obese group 19.0-29.9	Obese group 30.0-76.0	P
<i>n</i>	38	153	
Age (years)	43 ± 13	45 ± 12	0.399
Male (<i>n</i> (%))	15 (39.5)	64 (41.8)	0.793
BMI (kg/m ²)	25.5 ± 3.3	41.2 ± 8.7	<0.001
Weight (kg)	75.5 ± 11.9	121.7 ± 27.7	<0.001
Height (cm)	171.9 ± 9.8	171.9 ± 10.5	1.000
Waist (cm) males	92.1 ± 8.5	131.5 ± 17.8	<0.001
Waist (cm) females	84.6 ± 10.0	114.3 ± 17.6	<0.001
Hip (cm) males	103.2 ± 5.4	130.6 ± 20.3	<0.001
Hip (cm) females	103.4 ± 9.0	132.6 ± 16.1	<0.001
Waist/Hip-Ratio males	0.89 ± 0.05	1.01 ± 0.08	<0.001
Waist/Hip-Ratio females	0.82 ± 0.06	0.86 ± 0.07	0.009
HR (beats/minute)	67 ± 14.0	72 ± 13.3	0.043
SBP (mmHg)	132 ± 15	139 ± 19	0.022
DBP (mmHg)	83 ± 9	90 ± 13	0.003
Fasting glucose (mg/dL)	85 ± 10	98 ± 24	<0.001
Fasting insulin (μU/mL)	9.0 ± 6.1	25.1 ± 24.8	<0.001
HOMA-IR	2.0 ± 1.5	6.4 ± 7.3	<0.001
Triglycerides (mg/dL)	123 ± 80	150 ± 84	0.069
HDL (mg/dL) males	55 ± 11	39 ± 7	<0.001
HDL (mg/dL) females	68 ± 24	53 ± 14	<0.001
NT-proBNP (pg/mL)	57 ± 51	61 ± 71	0.711
GDF15 (pg/mL)	478 ± 175	634 ± 271	<0.001
6mWT (m)	629 ± 98	548 ± 107	<0.001

Values represent the mean ± standard deviation or numbers (percentages). BMI indicates body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA, Homeostasis Model Assessment; HDL, high density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; GDF15, growth differentiation factor 15; and 6mWT, 6 minute walking test.

Table II. Echocardiographic Parameters of Non-Obese and Obese Subjects

BMI (kg/m ²)	Non-obese group 19.0-29.9	Obese group 30.0-76.0	P
<i>n</i>	38	153	
LAD (mm)	36.6 ± 7.3	41.6 ± 6.2	<0.001
LAA (mm ²)	15.8 ± 3.7	19.8 ± 4.3	<0.001
LVEDD (mm)	48.1 ± 8.4	51.2 ± 7.4	0.023
LVESD (mm)	28.9 ± 5.8	31.9 ± 5.5	0.004
IVS (mm)	9.4 ± 1.5	11.2 ± 2.0	<0.001
PW (mm)	8.9 ± 1.3	10.5 ± 1.6	<0.001
LVM (g/m ²)	107 ± 23	119 ± 29	0.026
RWT	0.36 ± 0.05	0.41 ± 0.06	<0.001
EF (%)	68.9 ± 6.3	65.9 ± 5.5	0.004
FS (%)	39.6 ± 7.0	37.8 ± 5.7	0.165
DT (ms)	209 ± 44	202 ± 70	0.581
E/A	1.41 ± 0.58	1.18 ± 0.36	0.003
E'	14.2 ± 6.7	11.9 ± 3.9	0.006
E/E'	6.3 ± 2.6	7.4 ± 2.5	0.010
E'/A'	1.6 ± 0.7	1.3 ± 0.6	0.011
RV TAPSE (mm)	25.1 ± 3.5	25.6 ± 4.5	0.528
TDI S' (cm/second)	13.8 ± 2.9	13.5 ± 2.9	0.553
TEI	0.28 ± 0.09	0.25 ± 0.13	0.283
RAA (mm ²)	16.6 ± 4.2	17.9 ± 3.6	0.188
RVEDD (mm)	31.6 ± 3.7	31.5 ± 5.4	0.952
RVESD (mm)	21.4 ± 4.2	21.7 ± 4.5	0.854
PAP (mmHg) in presence of TR	22.7 ± 2.9	22.4 ± 7.7	0.921

Values represent the mean ± standard deviation. LAD indicates left atrial diameter; LAA, left atrial area; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVS, interventricular septum thickness; PW, posterior wall; LVM, left ventricular mass; RWT, relative wall thickness; EF, ejection fraction; FS, fractional shortening; DT, deceleration time; E, early diastolic mitral inflow; A, late diastolic mitral inflow; E', early diastolic mitral annular tissue velocity; A', late (atrial contraction) diastolic mitral annular tissue velocity; TAPSE, tricuspid annular plane systolic excursion; TDI S', tricuspid annular systolic velocity; TEI, myocardial performance index; RAA, right atrial area; RVEDD, right ventricular end-diastolic diameter; RVESD, right ventricular end-systolic diameter; PAP, pulmonary artery pressure; and TR, tricuspid regurgitation.

Table III. Right Ventricular Echocardiographic Parameters Across Increasing Body Mass Index (BMI) Categories

BMI (kg/m ²)	19.0-25.0	25.1-30.0	30.1-35.0	35.1-40.0	> 40.0	<i>P</i>
mean	22.3 ± 1.3	28.1 ± 1.5	32.4 ± 1.5	37.6 ± 1.4	48.8 ± 7.3	
<i>n</i>	17	21	43	40	70	
RV TAPSE (mm)	24.7 ± 4.0	25.5 ± 3.1	24.8 ± 2.8	25.7 ± 3.5	26.1 ± 5.7	0.467
TDI S' (cm/second)	14.7 ± 3.1	13.1 ± 2.6	12.4 ± 1.7	14.4 ± 2.0	13.8 ± 3.6	0.448
RV TEI	0.29 ± 0.08	0.26 ± 0.09	0.27 ± 0.14	0.27 ± 0.11	0.24 ± 0.12	0.568
RAA (mm ²)	14.4 ± 1.8	17.4 ± 4.5	17.0 ± 3.3	17.2 ± 3.4	19.1 ± 3.6	0.052
RVEDD (mm)	30.8 ± 2.1	31.8 ± 4.2	30.5 ± 5.4	30.7 ± 3.1	32.7 ± 6.2	0.440
RVESD (mm)	19.0 ± 1.4	22.3 ± 4.5	21.3 ± 4.7	21.0 ± 3.0	22.3 ± 5.0	0.521
PAP (mmHg)	22.3 ± 2.9	23.0 ± 3.3	20.8 ± 5.0	26.6 ± 5.7	20.5 ± 10.7	0.611

Values represent the mean ± standard deviation. *P*-values for comparison of the different BMI groups were determined by using the analysis of variance (ANOVA). Abbreviations as in Table II.

Table IV. Right Ventricular Parameters in Comparison to Participants With and Without the Metabolic Syndrome

	Non obese (BMI < 30.0 kg/m ²)	Obese without metabolic syndrome	Obese with metabolic syndrome	<i>P</i>
<i>n</i>	38	75	78	
RV TAPSE (mm)	25.1 ± 3.5	25.0 ± 3.9	26.3 ± 5.0	0.126
TDI S' (cm/second)	13.8 ± 2.9	13.0 ± 2.2	14.0 ± 3.3	0.146
TEI	0.28 ± 0.09	0.25 ± 0.11	0.26 ± 0.10	0.990
RAA (mm ²)	16.6 ± 4.2	17.4 ± 3.6	18.3 ± 3.5	0.532
RVEDD (mm)	31.6 ± 3.7	31.1 ± 5.4	31.9 ± 5.3	0.759
RVESD (mm)	21.4 ± 4.2	21.2 ± 4.7	22.0 ± 4.2	0.640
PAP (mmHg)	22.7 ± 2.9	16.8 ± 6.6	22.7 ± 8.3	0.069

The metabolic syndrome was defined according to the NCEP ATP III-criteria.¹⁰⁾ Values represent the mean ± standard deviation. *P*-values for comparison between obese with and without the metabolic syndrome were determined by using the Student's *t*-test for normally distributed data and the Mann-Whitney *U* test for skewed data, adjusting for age and sex. Abbreviations as in Table II.

for normally distributed data and the nonparametric Wilcoxon signed rank test for skewed data were used for the analysis of repeated measures (between pairs of values before and after weight reduction). The concordance correlation coefficient, a measure of precision and accuracy¹⁵⁾ to describe inter-observer variability, for 20 duplicate measurements was 0.91 ± 0.03 for TAPSE, 0.95 ± 0.02 for TDI S', and 0.84 ± 0.08 for RV-TEI indicating high reproducibility of these Doppler parameters. Statistical significance was considered at the 0.05 level.

RESULTS

Baseline characteristics of the study population: Baseline characteristics of the study population are described in Table I. In addition to predefined higher levels of BMI and associated obesity parameters, all components of the metabolic syndrome were significantly different with higher systolic and diastolic blood pressure levels, higher blood glucose levels, higher HOMA (Homeostasis Model Assessment) index-levels, higher triglyceride levels, and lower HDL cholesterol levels in the obese. Furthermore, obese participants covered a shorter distance in the 6-minute walking test (6 MWT). Moreover, novel cardiac stress biomarkers, such as GDF15-levels, were higher in the obese subjects.

Echocardiographic characteristics at baseline: Echocardiographic parameters of the study population are displayed in Table II. Parameters of left ventricular size and geometry were significantly higher in the obese, and several parameters of

systolic and diastolic left ventricular function were more impaired in the obese. In contrast, the right ventricular function parameters TAPSE (25.6 ± 4.5 versus 25.1 ± 3.5 mm, *P* = 0.528), TDI S' (13.5 ± 2.9 versus 13.8 ± 2.9 mm/second, *P* = 0.553), and TEI (0.25 ± 0.13 versus 0.28 ± 0.09, *P* = 0.283) were almost identical in obese and non-obese participants. Furthermore, the parameters of right atrial and right ventricular size were comparable in both groups (Table II). In subjects with tricuspid regurgitation, systolic pulmonary pressure was similar in the obese (22.4 ± 7.7 mmHg) and non-obese (22.7 ± 2.9 mmHg, *P* = 0.921).

In Table III, parameters of right ventricular and right atrial geometry as well as right ventricular functional parameters are shown across increasing BMI categories. No significant association between these right heart parameters and increasing BMI categories could be assessed. Even in the group of morbid obese subjects (BMI > 40.0 kg/m², *n* = 70) no statistical significant differences in right ventricular function parameters were obvious compared to non-obese subjects.

About half of the obese subjects (78 of 153) were affected by the metabolic syndrome, as defined by the NCEP ATP III-criteria. However, the presence of the metabolic syndrome did not appear to alter right ventricular function and geometry (Table IV).

RV Dysfunction: Only 7 of the 153 obese participants (4.6%) had evidence of impaired RV function according to our pre-specified criteria.

BMI, blood pressure levels, HOMA, insulin and glucose levels, as well as heart rate were higher in the group with than

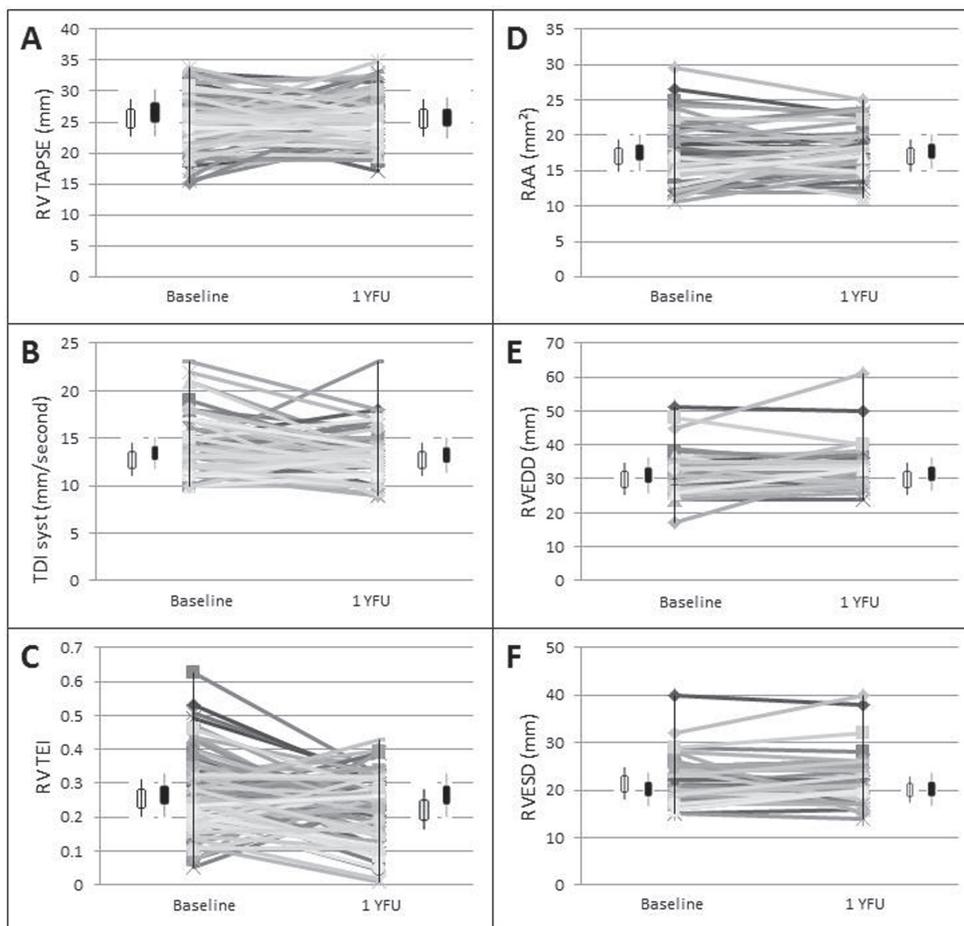


Figure. Effects of weight reduction on echocardiographic parameters of RV function and geometry. The graph represents the change in individual samples. In addition, the bars represent the mean \pm standard deviation. The paired *t*-test and the nonparametric Wilcoxon signed rank test were used for the analysis of repeated measures. Data are displayed from baseline (before weight reduction) to one year of follow up (1 YFU) in all study participants (Φ) as well as in subjects with successful weight reduction (\bullet). No statistically significant differences between the groups could be detected. **A:** RV TAPSE, **B:** TDI syst, **C:** RV TEI, **D:** RAA, **E:** RVEDD, **F:** RVESD.

without RV dysfunction. Markers of heart failure such as NT-pro-BNP and GDF-15 levels and the 6 MWT distance were similar in the group of participants with impaired RV function and normal function.

However, due to its small sample size, this group with impaired RV function did not allow statistically meaningful associations or appropriate conclusions on the relation between RV function and metabolic state.

Successful weight reduction: After participation in the 1-year weight reduction program, 40.5% of the remaining obese subjects achieved successful weight reduction while 59.5% did not. Average reduction of BMI was -7.71 kg/m^2 in the group with successful weight loss, and $+0.10 \text{ kg/m}^2$ in the group without successful weight reduction. Participants with and without successful weight reduction showed no significant differences in baseline BMI, gender distribution, and age. RV TAPSE, TDI S', and TEI levels as well as right heart geometry parameters showed no significant differences between the groups of successful and failed weight reduction either at the beginning or at the end of the program (Figure, Supplemental

Table I). Moreover, weight loss did not influence these parameters within the group of successful weight reduction (Figure).

Weight reduction to a BMI $< 30 \text{ kg/m}^2$ after one year was achieved by 23 obese participants. Right function parameters were similar before and after weight reduction in this group, equally RAA and RVESD. RVEDD was higher after weight reduction (Supplemental Table II).

DISCUSSION

The aim of the present study was to examine the relationship between obesity with and without the metabolic syndrome and RV function and right heart dimensions. In our study of subjects with morbid obesity (with a mean BMI of $41.2 \pm 8.7 \text{ kg/m}^2$), parameters of RV function and dimension of right heart chambers were comparable to non-obese subjects (with a mean BMI of $25.5 \pm 3.3 \text{ kg/m}^2$). Indeed, even extremely obese subjects (with BMI $> 40 \text{ kg/m}^2$) had no greater impairment of RV function according to TAPSE, tissue Doppler systolic ex-

cursion velocity, and myocardial performance index TEI compared to non-obese participants. In contrast, parameters of left ventricular size and function were significantly altered in the obese. However, it should be mentioned that the few obese subjects who were identified with RV dysfunction presented with a higher BMI and more pronounced metabolic syndrome parameters such as higher fasting insulin/glucose levels and higher blood pressure levels than obese subjects with normal RV function.

In the literature, the relation between adiposity and RV function remains controversial. In the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter prospective cohort study designed to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in individuals without previous clinical cardiovascular disease, a subgroup of 4127 participants underwent cardiac magnetic resonance imaging with interpretable data on right ventricular geometry.¹⁶ Although this study demonstrated larger RV volumes, increased RV mass, and lower RV ejection fraction (RVEF) in the obese independent of pulmonary function, other comorbidities, and respective changes in the left ventricle, it is questionable whether these statistically significant, but small morphological changes (that may have only been detected by MRI) have clinical implications. Indeed, RVEF was quite similar and on average remained normal in obese (71.8%) and lean subjects (72.6%). Moreover, guideline-recommended quantitative echocardiographic assessment of RV function, including TAPSE, TEI, or TDI as well as pulmonary artery pressures were not assessed in this study.¹³ Thus, despite the certainly valuable data obtained from this large community-based MRI study, it is still unclear whether the frequency of RV dysfunction is really higher in obese than in lean individuals. Moreover, it has not been investigated so far whether weight loss would reverse the effects on the right ventricle in the obese.

Obese subjects were also found to have echocardiographic abnormalities of RV function when compared to a non-obese control group in a small study.¹⁷ In this study, significant impairment of both LV and RV systolic function in obese subjects was detected using strain rate imaging, although several conventional and TDI echocardiographic systolic parameters did not show any statistically significant differences between the obese and non-obese groups. This has been explained by the relative insensitivity of conventional and TDI-derived echocardiographic methods that may not be able to detect early abnormalities in longitudinal function, in contrast to strain rate imaging methods.¹⁸⁻²³ However, the implied superiority of strain imaging emerged almost exclusively from examinations of the left ventricle^{18-20,24} which may not be simply transferred to the right ventricle. Moreover, although regional RV strain represents a potential means to assess myocardial contractility that is less load-dependent, there is still a lack of normative data and the measure is angle dependent with a poor-signal-to-noise ratio.¹³ Thus, strain rate imaging has a high degree of variability that may be particularly evident in severely obese candidates limiting the clinical use of this complex measure.

In contrast to the above mentioned results, we and others^{17,25,26} have found no association of RV function and increasing BMI in obese and/or overweight persons. Additionally, right atrial and right ventricular end-systolic and diastolic dimensions, as well as RV diastolic function did not differ significantly across increasing BMI categories.^{17,25,26} On the other

hand, these studies consistently found significant alterations of LV parameters, implying more sensible adaptations of the left than the right heart to increasing adiposity.

The reasons for the incongruent study results remain speculative. In theory, right ventricular changes in cardiovascular structure, function, and hemodynamics in obese subjects may occur through multifactorial mechanisms.⁷ Obesity is associated with intravascular volume overload, consequently increasing cardiac output, ventricular wall stress, LV hypertrophy, and myocardial oxygen consumption. These cardiovascular adaptations may further increase pulmonary vascular resistance leading to RV remodeling and hypertrophy.^{1,5,6} This progression is probably a prolonged process which might explain the lack of functional adaptations in our relatively young study population. Notably, in the above mentioned study by Orhan, *et al*, duration of obesity was particularly associated with impaired RV function.¹⁷

In this small study, TDI S' was slightly lower in the obese compared to controls. However, mean TDI S' was within the normal range and RV TAPSE levels were similar in obese and non-obese subjects. Thus, these data may not show compelling evidence of impaired RV function in the obese.¹⁷

An additional reason responsible for right heart structural and functional changes are obesity-related comorbidities such as obstructive sleep apnea syndrome (OSA), frequently present in subjects with severe obesity.^{5,7} As a consequence of OSA and obesity hypoventilation syndrome, RV dilation could be induced by an increase in oxygen consumption and hypoxia.^{5,27,28} In these cases, impaired RV function is seen independently of pulmonary hypertension.²⁹⁻³¹ Indeed, available data on impaired RV function of obese patients were frequently acquired from predominantly severely obese patients, who also have concomitant OSA. However, a positive correlation of sleep breathing disorder with right ventricular wall thickness was described without significant differences in right atrial dimensions, RV dimensions, and RV systolic function.³⁰

In a study by Wong, *et al* obesity was associated with decreased TDI S' levels but around 30% of obese study participants had obstructive sleep apnea and off-line analysis by color-coded tissue Doppler was used, limiting interpretation of these data to some extent.¹⁰

Furthermore, a direct myocardial lipid infiltration has been described which has cardiotoxic effects and causes structural and functional cardiac changes predisposing to LV hypertrophy and non-ischemic dilated cardiomyopathy.³² Lipid accumulation is associated with a growing degree of adiposity and may also interfere with RV function. In addition, changes in adipokine levels have been described in association to obesity,³³ but these effects have only been demonstrated for LV hypertrophy.^{33,34} However, the results of our study demonstrate that these effects on RV function are too small to detect or have no clinical relevance.

Furthermore, other risk factors for ventricular dysfunction such as hypertension, hyperlipidemia, and diabetes mellitus are provoked by obesity. However, in our study no differences in RV function could be demonstrated when comparing healthy subjects and participants with metabolic disorder in contrast to LV function. Although the obese participants were older, had higher systolic and diastolic blood pressure, more diabetes mellitus, and higher triglyceride levels, they did not present more frequently with RV dysfunction. This fact mainly sug-

gests an association between these cardiovascular risk factors and LV function or only minimal-structural RV changes that are not detected in echocardiographic examination. Again, minimal structural changes in the right ventricle may only be detected by MRI measurement, as it was done in the above mentioned MESA study.¹⁶⁾

In the comparison of participants with successful and failed weight reduction, RV function as well as right heart geometry parameters did not differ either at the beginning or at the end of the program in our study population. The participants with successful weight reduction including participants with weight reduction to a BMI < 30 kg/m² achieved an impressive weight loss without a meaningful influence on RV function. Nevertheless, we do not know whether stronger weight reduction (ie, to normal weight levels) or maintaining the achieved weight loss for more than one year affect RV parameters to a greater extent. In this regard further prospective patient studies are warranted.

Limitations: Several factors limit our study results. First, the method of recruitment of the study participants may have led to selection bias. Secondly, a large variability in echocardiographic measurements could be responsible for the lack of an association between obesity and right ventricular dysfunction, especially as a consequence of limited testing conditions in extremely obese subjects. However, the concordance for 20 duplicate measurements of two expert echocardiographers was very high. Third, right ventricular diastolic function, which could indicate early abnormalities of right ventricular structure and function corresponding to the left side, was not measured in our study. Fourthly, we do not know the exact duration of obesity in our study participants. The duration of obesity was an independent predictor for an impaired right ventricular function in one¹⁷⁾ but not all studies.¹⁰⁾ Finally, screening for obstructive sleep apnea and correlation to right ventricular parameters were not carried out in our collective.

Conclusion: The results show no clinically relevant differences in right ventricular function across different grades of human obesity, and no differences in comparison to participants with the metabolic syndrome. Further analyses in a larger group of subjects with RV function should be conducted to re-analyze the relationship to obesity and metabolic alterations.

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DISCLOSURE

Conflict of interest: The authors declare there are no conflicts of interest.

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SUPPLEMENTAL FILES

Supplemental Table I, II

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