Characterization of tricuspid regurgitation and its prognostic implications

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Chapter 7

The obesity paradox in patients with significant tricuspid regurgitation: effects of obesity on right ventricular remodeling and long-term prognosis

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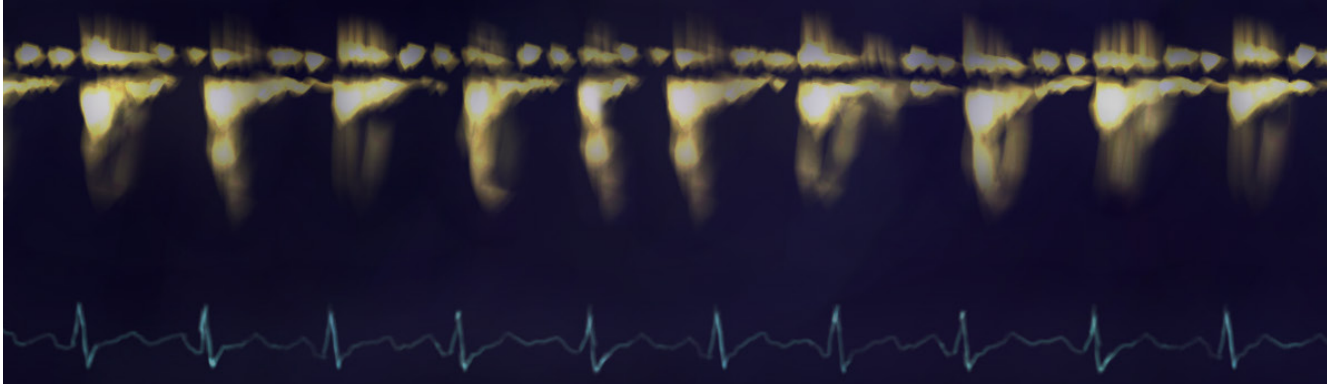


ABSTRACT

Background: Obesity may cause right ventricular (RV) remodeling due to volume overload. However, obesity is also associated with better prognosis compared to normal weight patients in various cardiac diseases.

Objective: The aim of this study was to assess the impact of obesity on RV remodeling and long-term prognosis in patients with significant (moderate and severe) tricuspid regurgitation (TR).

Methods: A total of 951 patients with significant TR (age 70 [61-77] years, 50% male) were divided into 3 groups according to body mass index (BMI): normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (BMI≥30 kg/m^2). Patients with congenital heart disease, peripheral edema, active endocarditis and BMI<18.5 kg/m^2 were excluded. RV size and function for each group were measured by transthoracic echocardiography and compared to reference values of healthy study populations. The primary endpoint was all-cause mortality. Event rates were compared across the 3 BMI categories.

Results: 476 (50%) patients with significant TR had a normal weight, 356 (37%) were overweight and 119 (13%) patients were obese. RV end-diastolic and end-systolic areas were larger in overweight and obese patients compared to normal weight patients. However, no differences in RV systolic function were observed. During a median follow-up of 5 years, 358 (38%) patients died. Five-year survival rates were significantly better in overweight and obese patients compared to patients with normal weight (65% and 67% compared to 58%, respectively, p<0.001 and p=0.005). In multivariable analysis, overweight and obesity were independently associated with lower rates of all-cause mortality compared to normal weight (HR, 0.628; 95% CI, 0.493-0.800 and HR, 0.573, 95% CI 0.387-0.848, respectively).

Conclusion: In patients with significant TR, overweight and obese patients demonstrated more RV remodeling compared to patients with normal weight. Nevertheless, a higher BMI was independently associated with better long-term survival, confirming the obesity paradox in this context.

INTRODUCTION

Obesity is a rapidly growing problem in the modern society and a known risk factor for the development of heart failure (1). Hemodynamic and metabolic changes due to excessive adipose tissue in patients with a high body mass index (BMI) may increase total blood volume and cardiac output (2). The resulting pressure and volume overload are associated with various changes in cardiac morphology and function in the general community, including right ventricular (RV) dilation and dysfunction (3). By a similar mechanism, significant (moderate or severe) tricuspid regurgitation (TR) causes volume overload of the RV and is often associated with RV dilation and/or dysfunction at first presentation (4). Whether a high BMI enhances RV remodeling and dysfunction in patients with significant TR has never been investigated.

Several studies have demonstrated the independent influence of RV dysfunction on prognosis in patients with significant TR (4, 5). The association between high BMI and RV dysfunction in different patient populations would suggest that obesity enhances the development of RV dysfunction and has a negative effect on prognosis in patients with significant TR (3, 6). However, in patients with certain established cardiovascular diseases, a higher BMI is associated with lower mortality, known as the obesity paradox (7). No studies to date have investigated if the obesity paradox exists in patients with significant TR.

More insight into the effects of BMI on RV remodeling and function and the influence on prognosis in patients with significant TR is needed. Therefore, the aim of the current study was to assess the impact of overweight and obesity on RV remodeling and long-term prognosis in a large cohort of patients with significant TR.

METHODS

Patients

A query was performed in the departmental echocardiographic database of the Leiden University Medical Center (Leiden, the Netherlands) whereby 1,598 patients with significant (moderate and severe) TR between June 1995 and September 2016 were selected. TR was diagnosed by a multiparametric approach in agreement with current recommendations, including qualitative, semi-quantitative and quantitative data of the regurgitant jet, tricuspid valve characteristics, right atrial (RA) and RV size (8, 9). Patients with congenital heart disease, previous tricuspid valve surgery or endocarditis of the tricuspid valve at baseline were excluded. For inclusion in the present study, patients were

required to have height and weight data documented at the time of first echocardiographic diagnosis of significant TR to derive baseline BMI by the following formula: body weight (kg) divided by height squared (m^2). Those patients with peripheral edema at baseline, which could lead to incorrect BMI measurements, were excluded. Patients were divided into BMI categories according to current guidelines (10). Because of the small number of underweight patients in the current database, 3 BMI categories were examined and compared in the final study population: patients with normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) (Figure 1).

The first transthoracic echocardiogram diagnosing significant (moderate and severe) TR marked the baseline time point for the subsequent survival analyses. Demographic and clinical data at baseline were collected retrospectively in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center). Clinical characteristics included New York Heart Association (NYHA) functional class, cardiovascular risk factors, relevant comorbidities, laboratory values and medication use. The institutional review board of the Leiden University Medical Center approved the observational design of the current retrospective study of clinically acquired anonymized data and waived the need for written informed consent of the patients.

Echocardiography

Transthoracic 2-dimensional echocardiography was performed according to current recommendations (8, 11). Commercially available ultrasound systems (Vivid 7, E9 and E95 systems; GE-Vingmed) equipped with 3.5 MHz or M5S transducers were used. Images were digitally stored for offline analysis using EchoPAC version 113.0.3 and 202 software (GE-Vingmed, Horten, Norway). M-mode, bidimensional and color, continuous- and pulsed-wave Doppler data were obtained from parasternal long- and short-axis, apical and subcostal views. Left ventricular (LV) ejection fraction was derived from LV end-diastolic and end-systolic volumes measured on apical 2- and 4-chamber views by the Simpson method (11). The peak velocity of the early diastolic flow (E) and late diastolic flow (A) across the mitral valve in patients with sinus rhythm were measured and the E/A ratio was derived (12). Significant (moderate or severe) aortic stenosis was defined by an aortic valve area ≤ 1.5 cm^2 as calculated using the continuity equation (13). Mitral regurgitation and TR were assessed based on qualitative, semi-quantitative and quantitative measurements evaluated on bidimensional, color, continuous and pulsed wave Doppler data and graded according to current recommendations (8). All dimensions and areas of the RA, RV and the tricuspid valve annulus were measured on the RV focused apical 4-chamber view. RV systolic pressure was estimated based on the TR peak jet velocity with continuous wave

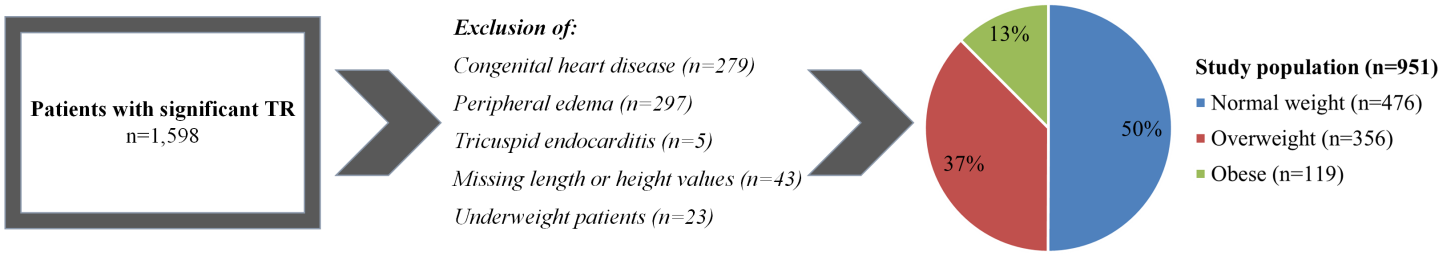


Figure 1. Flowchart of the selection of the study population and the distribution of body mass index categories in patients with significant tricuspid regurgitation

TR= tricuspid regurgitation

Doppler using the modified Bernoulli equation (14). RV systolic function was assessed by tricuspid annular plane systolic excursion (TAPSE), which was measured on M-mode recordings of the lateral tricuspid annulus in an RV focused apical 4-chamber view. Additionally, fractional area change was derived from RV end-diastolic and end-systolic areas (11). From the RV focused apical view, 2-dimensional RV free wall longitudinal strain was measured and calculated as the mean of the RV lateral basal, mid and apical segments and values are presented as absolute values (15). All left and right atrial and ventricular dimensions, areas and volumes were corrected for height for comparison across BMI categories. Furthermore, median RV end-diastolic areas of all groups were compared to reference values of the current recommendations, the Atherosclerosis Risk in Communities (ARIC) study and the Coronary Artery Risk Development in Young Adults (CARDIA) study, to define RV remodeling in patients with TR (3, 11, 16).

Outcome

Patient follow-up started on the day of first diagnosis of significant TR by echocardiography. The primary endpoint for the current study was all-cause mortality. Date of death was ascertained from the departmental Cardiology Information System and the Social Security Death Index and was available for all patients. Secondary endpoints were hospitalization for heart failure, tricuspid valve surgery and any other valve surgery and were obtained from the departmental Cardiology Information System.

Statistical analysis

Continuous variables with Gaussian distribution are presented as mean ± standard deviation. Non-normally distributed continuous variables are presented as median (interquartile range [IQR]). Categorical variables are presented as frequencies and percentages. Differences between BMI categories were analyzed using the one-way analysis of variance for continuous variables in case of Gaussian distribution, the Kruskal-Wallis test for continuous variables in case of non-Gaussian distribution and the Pearson χ^2 test for categorical variables. Post hoc correction for multiple comparisons between groups was performed by the Bonferroni method.

Kaplan-Meier curves were used to estimate cumulative 1- and 5-year survival rates. Differences between BMI categories were compared using the log-rank test. Likewise, Kaplan-Meier curves were composed for the combined endpoint of all-cause mortality and hospitalization for heart failure. Cox proportional hazards models were used to investigate the independent associates of all-cause mortality and of the combined endpoint of all-cause mortality and hospitalization for heart failure. Clinical and echocardiographic variables that were different between BMI categories at baseline and possible confounders

for the association between BMI and mortality in patients with TR were included in the univariable analysis. Variables with a P-value <0.1 in the univariable analysis were considered significant for entry in the multivariable analysis. A tolerance level of >0.5 was set to avoid multicollinearity between the univariable determinants. No collinearity was detected, thus all parameters that were significantly associated with all-cause mortality in univariable analysis were included in the multivariable model. The proportional-hazards assumption was confirmed using statistics and graphs on the basis of the Schoenfeld residuals. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. All tests were 2-sided and P-values <0.05 were considered significant. Statistical analyses were performed with SPSS for Windows, version 25 (SPSS Inc, Armonk, NY:IBM Corp).

RESULTS

After the exclusion of patients with congenital heart disease (n=279), tricuspid valve endocarditis (n=5), peripheral edema (n=297), those with missing length or height values (n=43) and patients with a BMI <18.5 kg/m^2 (n=23), a total of 951 patients with significant TR were included in the final study population. In 49% of the cases, the patient was hospitalized at the time of the first diagnosis of significant TR. At the time of first diagnosis of significant TR, 476 patients (50%) had a normal weight, 356 patients (37%) were overweight and 119 (13%) patients were obese (Figure 1).

Clinical characteristics

The clinical characteristics of all patients and according to BMI categories are summarized in Table 1. The median age was 70 years (IQR 61-77) and 477 patients (50%) were male. Patients with significant TR were often limited in their physical activity, with 336 patients (39%) presenting in NYHA functional class III and IV heart failure symptoms. Pre-existing hypertension was common (81%) and approximately half of the patients had atrial fibrillation (48%).

In per-group analysis, obese patients were more often female (63%) and less tall (168 ± 9 cm) than those with normal weight (50% and 171 ± 10 cm, p=0.002 and p=0.003; respectively). Overweight and obese patients were more likely to have hypercholesterolemia and diabetes mellitus compared to patients with normal weight (p=0.009 and p<0.001, respectively). Furthermore, use of diuretics and statins was more prevalent in patients with a higher BMI (p=0.022 and p=0.015, respectively). No significant differences across BMI categories were observed in hemoglobin, creatinine and urea level.

Table 1. Baseline clinical characteristics of the overall population of patients with significant tricuspid regurgitation and according to body mass index

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Age, years	70 (61-77)	71 (60-78)	69 (61-77)	69 (59-75)	0.282
Male sex	477 (50)	236 (50) ‡	197 (55) ‡	44 (37) *†	**0.002**
Weight, kg	75 ± 14	67 ± 10 †‡	80 ± 9 *‡	94 ± 12 *†	**<0.001**
Height, cm	171 ± 10	171 ± 10 ‡	172 ± 10 ‡	168 ± 9 *†	**0.003**
BSA, m^2	1.9 ± 0.2	1.8 ± 0.2 †‡	2.0 ± 0.2 *‡	2.1 ± 0.2 *†	**<0.001**
BMI, kg/m^2	26 ± 4	23 ± 2 †‡	27 ± 1 *‡	33 ± 3 *†	**<0.001**
NYHA class >II	336 (39)	160 (38)	126 (38)	50 (47)	0.175
Hypertension	714 (81)	354 (80)	266 (80)	94 (85)	0.532
Hypercholesterolemia	419 (47)	187 (42) †‡	171 (52) *	61 (55) *	**0.009**
Diabetes mellitus	148 (17)	51 (12) †‡	59 (18) *‡	38 (34) *†	**<0.001**
(Ex-)smoker	271 (31)	131 (30)	109 (33)	31 (28)	0.571
Coronary artery disease	362 (38)	169 (36)	147 (42)	46 (39)	0.264
Pacemaker/ICD	348 (37)	167 (36)	138 (39)	43 (36)	0.625
Atrial fibrillation	421 (48)	204 (46)	159 (48)	58 (52)	0.528
Chronic obstructive pulmonary disease	114 (13)	58 (13)	42 (13)	14 (13)	0.987
Hemoglobin, mmol/L	8.0 (6.9-8.8)	8.1 (7.1-8.8)	8.0 (6.9-8.9)	7.7 (6.4-8.6)	0.071
Creatinine, µmol/L	89 (73-116)	89 (72-114)	90 (77-117)	88 (69-123)	0.145
Urea, mmol/L	8.1 (6.0-11.3)	8.1 (6.0-11.3)	8.2 (6.3-11.5)	7.8 (5.7-10.9)	0.446
Diuretics	495 (54)	226 (49)	199 (57)	70 (60)	**0.022**
Statins	401 (46)	180 (41) †	164 (50) *	57 (53)	**0.015**

*Values are mean ± SD, median (IQR), or n (%). P-value by Kruskal-Wallis or one way ANOVA for non-Gaussian and Gaussian distributed continuous variables, respectively. P-value by chi-square test for categorical variables (Bonferroni correction; *p < 0.05 vs. normal weight, †p < 0.05 vs. overweight, ‡p < 0.05 vs. obese).*

BMI = body mass index; BSA = body surface area; ICD = implantable cardiac defibrillator; IQR = interquartile range; NYHA = New York Heart Association; SD = standard deviation

Echocardiographic characteristics

Table 2 summarizes the echocardiographic characteristics of the total population and the comparisons across BMI categories. The mean LV ejection fraction of the overall population was 45 ± 15% and highest in obese patients (48 ± 14%, p=0.041). Concomitant significant aortic stenosis or mitral regurgitation was present in 180 (21%) and 249 patients (26%), respectively.

After correction for height, patients with overweight had larger LV end-diastolic and end-systolic volumes compared to patients with normal weight and obesity (p=0.006 and p=0.003, respectively). In contrast, RV end-diastolic and end-systolic areas were significantly larger in both overweight and obese patients compared to those with normal weight (p<0.001). RV systolic function as measured by TAPSE was reduced in the overall study population (16 ± 5 mm) and did not differ significantly across BMI categories (p=0.153). In contrast, RV free wall strain was significantly more impaired in obese patients compared to patients with normal weight and overweight. The tricuspid annulus diameter and RV linear diameters as well as the left and right atrium were largest in obese patients.

Quantitative data on TR severity were available for 852 patients. Overweight and obese patients had more severe TR compared to normal weight patients based on quantitative parameters, but not according to the multiparametric approach (Table 2). A sensitivity analysis was performed to assess the relationship between BMI and RV size in different TR grades based on effective regurgitant orifice area (EROA). In patients with quantitatively assessed severe TR (EROA≥40mm^2), a similar progression of RV end-diastolic area along with increasing BMI was demonstrated as in the overall population (Supplemental Table 1).

RV remodeling according to BMI in patients with significant TR

According to the most recent recommendations, the normal range for RV end-diastolic area when indexed to body surface area (BSA) is 4.5-11.5 cm^2/m^2 for women and 5-12.6 cm^2/m^2 for men (11). Similar 95% reference limits were reported in the Coronary Artery Risk Development in Young Adults (CARDIA) study by Ogunyankin et al. (16) including a large population of healthy young adults. In the current study of patients with significant TR, RV dilation was frequent: median RV end-diastolic area of 11.5 cm^2/m^2 (IQR 9.3-14.0) for women and 12.9 cm^2/m^2 (IQR 10.8-16.0) for men. Linear dimensions also showed RV basal (47 ± 8 mm) and midventricular (36 ± 9 mm) dilation, as compared to current limits of normality (25-41 mm and 19-35 mm, respectively) (11). In contrast, the mean longitudinal diameter of the RV in patients with significant TR (75 ± 12 mm) was within the normal range summarized in the guidelines (59-83 mm) (11).

Table 2. Baseline echocardiographic characteristics of the overall population of patients with significant tricuspid regurgitation and according to body mass index

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Heart rate, bpm	78 ± 18	79 ± 17	77 ± 18	80 ± 19	0.183
LV end-diastolic volume/height, mL/m	65 (47-97)	63 (45-91) †	69 (50-104) *	65 (46-94)	**0.006**
LV end-systolic volume/height, mL/m	34 (22-58)	32 (21-54) †	38 (24-68) *	31 (23-51)	**0.003**
LV ejection fraction, %	45 ± 15	46 ± 15	44 ± 15 ‡	48 ± 14 †	**0.041**
E/A ratio	1.5 (1.0-2.6)	1.3 (0.9-2.5)	1.6 (1.1-2.7)	1.8 (1.2-2.8)	**0.026**
LA maximum volume/height, mL/m	53 (34-75)	49 (33-74)	57 (36-74)	60 (39-78)	**0.029**
Significant aortic stenosis	180 (21)	94 (22)	65 (20)	21 (19)	0.715
Significant mitral regurgitation	249 (26)	128 (27)	97 (28)	24 (20)	0.273
Tricuspid annulus diameter/height, mm/m	24 ± 4	24 ± 5 ‡	25 ± 4	25 ± 4 *	**0.006**
RV basal diameter/height, mm/m	26 ± 5	26 ± 5	26 ± 4	27 ± 4	0.143
RV midventricular diameter/height, mm/m	20 ± 5	20 ± 5 ‡	20 ± 5	21 ± 5 *	**0.034**
RV longitudinal diameter/height, mm/m	42 ± 7	41 ± 6 †‡	42 ± 7 *	43 ± 7 *	**<0.001**
RV end-diastolic area/height, cm^2/m	13 (11-17)	13 (10-16) †‡	14 (11-17) *	15 (11-18) *	**<0.001**
RV end-systolic area/height, cm^2/m	8 (6-11)	8 (6-11) †‡	9 (7-12) *	9 (7-12) *	**<0.001**
RV systolic pressure, mmHg	32 (25-42)	31 (25-41)	33 (25-42)	33 (25-44)	0.615
RA maximum area/height, cm^2/m	15 (12-19)	15 (11-18) †‡	16 (12-20) *	16 (12-20) *	**0.001**
TAPSE, mm	16 ± 5	16 ± 5	15 ± 5	16 ± 5	0.153
RV fractional area change, %	36 ± 13	37 ± 13	35 ± 13	37 ± 12	0.310
RV free wall longitudinal strain (%)	15.6 ± 7.4	16.6 ± 7.3	15.5 ± 7.4	12.4 ± 7.1	**<0.001**
Severe tricuspid regurgitation	188 (20)	101 (21)	62 (17)	25 (20)	0.370
Leaflet tenting height, mm	10 (0-14)	8 (0-13) †‡	10 (0-15) *	12 (6-16) *	**<0.001**
PISA radius (mm)	12 ± 4	11 ± 4 †‡	12 ± 4 *	13 ± 4 *	**<0.001**
EROA (mm^2)	68 (45-102)	61 (42-93) †‡	72 (47-109) *	75 (49-131) *	**0.001**
RVol (ml/beat)	66 (41-102)	58 (37-91) †‡	71 (45-108) *	77 (47-120) *	**<0.001**

*Values are mean ± SD, median (IQR), or n (%). P-value by Kruskal-Wallis or one way ANOVA for non-Gaussian and Gaussian distributed continuous variables, respectively. P-value by chi-square test for categorical variables (Bonferroni correction; *p < 0.05 vs. normal weight, †p < 0.05 vs. overweight, ‡p < 0.05 vs. obese).*
E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; EROA = effective regurgitant orifice area; IQR = interquartile range; LA = left atrial; LV = left ventricular; PISA = proximal isovelocity surface area; RA = right atrial; RV = right ventricular; RVol = regurgitant volume; SD = standard deviation; TAPSE = tricuspid annular plane systolic excursion

Table 3. Occurrence of the outcome parameters in the overall population and according to body mass index during follow-up

	Overall (n=951)	Normal weight (n=476)	Overweight (n=356)	Obese (n=119)	P-value
Death	358 (38)	200 (42)	120 (34)	38 (32)	**0.019**
Hospital admission for heart failure	144 (15)	66 (14)	61 (17)	17 (14)	0.412
Tricuspid valve surgery	76 (8)	36 (8)	27 (8)	13 (11)	0.451
Any valve surgery	111 (12)	55 (12)	38 (11)	18 (16)	0.439

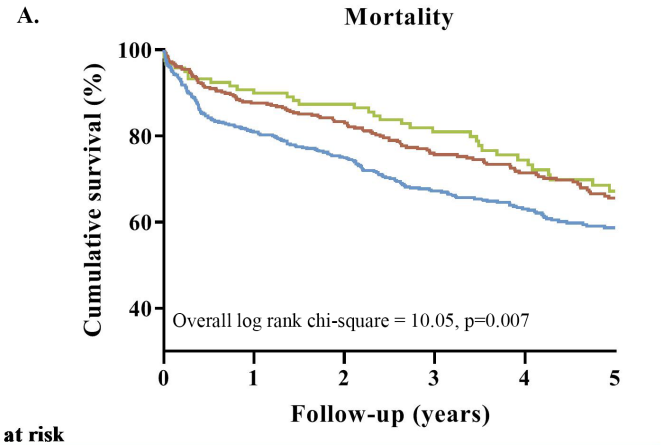
Values are n (%).

To the best of our knowledge, only the sub-study of the Atherosclerosis Risk in Communities (ARIC) trial (3) considered BMI to correct for cardiac abnormalities independent of comorbidities in obese patients in a population of 4343 patients aged 69-82 years who were free of coronary artery disease and heart failure. Overall, RV end-diastolic areas were larger in our population with significant TR (normal weight men, 25 cm^2 [IQR 20-31]; normal weight women, 19 cm^2 [16-24]) compared to patients in the ARIC study (normal weight men, 22 ± 5 cm^2; normal weight women; 16 ± 4 cm^2). The association between increasing BMI and larger RV end-diastolic area demonstrated in the ARIC study for both sexes is comparable to our findings: RV end-diastolic area in overweight men was 26 cm^2 (22-31) in patients with TR compared to 22 ± 5 cm^2 in patients of the ARIC sub-study and RV end-diastolic area in obese men was 28 cm^2 (23-37) compared to 23 ± 5 cm^2, respectively. In the current study, RV end-diastolic area was significantly larger in overweight and obese patients compared to normal weight patients in both men and women (p=0.005 and p<0.001, respectively).

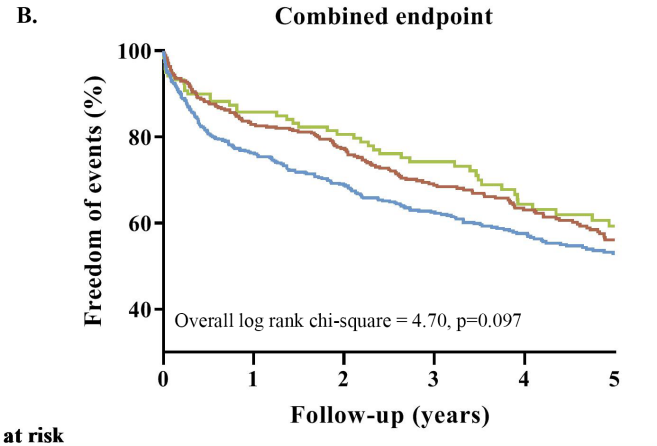
Long-term follow-up

During a median follow-up of 5 years (IQR 29-60 months), 358 patients (38%) died. In this period, 144 patients (15%) were hospitalized for heart failure. Only 76 patients (8%) received tricuspid valve annuloplasty or replacement while 111 out of 429 patients with concomitant valvular disease in this cohort had other valvular surgery during follow-up (Table 3). In the evaluation of outcome according to the BMI categories, the Kaplan-Meier analysis demonstrated a significant better survival for patients with overweight and obesity compared to those with normal weight (overall log rank Chi-square 10.05; p=0.007) (Figure 2A). One and 5-year survival rates were 81% and 58% in patients with normal weight, 87% and 65% in overweight patients, and 90% and 67% in obese patients, respectively. The Kaplan-Meier curves for the combined endpoint of all-cause mortality and hospital admissions for heart failure were similar across the BMI categories (overall log rank chi-square 4.70; p=0.097) (Figure 2B).

Univariable and multivariable Cox proportional hazard models for the primary endpoint are presented in Table 4. In multivariable analysis, overweight and obesity were independently associated with better survival compared to normal weight (HR, 0.628; 95% CI, 0.493-0.800; p<0.001 and HR, 0.573; 95% CI, 0.387-0.848; p=0.005, respectively). When introducing BMI as a continuous variable, higher BMI was also independently associated with better survival (HR, 0.934; 95% CI, 0.903-0.965; p<0.001). Additionally, older age, higher creatinine, diuretic use, larger LV end-diastolic volume and lower TAPSE were independently associated with all-cause mortality. Regarding the composite endpoint,



N. at risk						
Normal weight	476	381	318	235	177	138
Overweight	356	307	256	198	156	118
Obese	119	105	94	75	58	45



N. at risk						
Normal weight	476	363	309	248	189	143
Overweight	356	293	256	196	158	119
Obese	119	101	92	75	55	43

Figure 2. Kaplan-Meier curves for survival (A) and the combined endpoint of hospital admissions for heart failure and survival (B) according to body mass index in patients with significant tricuspid regurgitation

Table 4. Univariable and multivariable Cox proportional hazard models for mortality in patients with tricuspid regurgitation with BMI in categories (model 1) and BMI as continuous variable (Model 2)

Variable	Univariate analysis		Multivariate analysis – Model 1		Multivariate analysis – Model 2	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.024 (1.015-1.033)	**<0.001**	1.027 (1.017-1.037)	**<0.001**	1.026 (1.016-1.036)	**<0.001**
Male sex	1.290 (1.048-1.589)	**0.016**	1.010 (0.796-1.282)	0.936	0.988 (0.779-1.254)	0.924
Diabetes mellitus	1.702 (1.322-2.192)	**<0.001**	1.270 (0.951-1.696)	0.105	1.301 (0.977-1.733)	0.072
Hypercholesterolemia	1.074 (0.868-1.327)	0.512				
Creatinine	1.004 (1.003-1.005)	**<0.001**	1.003 (1.002-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**
Diuretics	1.931 (1.545-2.413)	**<0.001**	1.439 (1.118-1.852)	**0.005**	1.425 (1.106-1.836)	**0.006**
LV end-diastolic volume/ht	1.006 (1.004-1.008)	**<0.001**	1.004 (1.002-1.007)	**0.001**	1.004 (1.002-1.007)	**0.001**
LV ejection fraction	0.983 (0.977-0.990)	**<0.001**	0.994 (0.985-1.002)	0.132	0.994 (0.986-1.002)	0.159
E/A ratio	1.005 (0.989-1.022)	0.530				
TA diameter/ht	1.031 (1.007-1.056)	**0.013**	1.008 (0.982-1.035)	0.562	1.010 (0.983-1.037)	0.472
RV end-diastolic area/ht	1.010 (1.003-1.017)	**0.005**	1.006 (0.997-1.015)	0.190	1.006 (0.997-1.015)	0.226
TAPSE	0.952 (0.931-0.974)	**<0.001**	0.971 (0.948-0.995)	**0.017**	0.973 (0.950-0.997)	**0.026**
RV free wall longitudinal strain (each 1% decrease)	1.037 (1.020-1.054)	**<0.001**				
Severe TR	1.197 (0.933-1.535)	0.157				
BMI groups		**0.007**		**<0.001**	----------	-------
Normal weight (reference)	----------	-------	----------	-------	----------	-------
Overweight	0.734 (0.585-0.920)	**0.007**	0.628 (0.493-0.800)	**<0.001**	----------	-------
Obese	0.669 (0.473-0.947)	**0.023**	0.573 (0.387-0.848)	**0.005**	----------	-------
BMI (continuous)	0.951 (0.923-0.979)	**0.001**	----------	-------	0.932 (0.901-0.964)	**<0.001**

BMI = body mass index; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; ht = height; LV = left ventricular; RV = right ventricular; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation

multivariable analysis showed an independent association between overweight and obesity with better prognosis compared to normal weight (HR, 0.716; 95% CI, 0.573-0.895; p=0.003 and HR, 0.685; 95% CI, 0.483-0.971; p=0.034, respectively) (Supplemental Table 2).

DISCUSSION

The main findings of the current study of a large population of patients with moderate and severe TR are that a higher BMI is associated with a larger RV end-diastolic area, while no differences in RV systolic function were observed across BMI groups. In addition, overweight and obesity were independently associated with lower all-cause mortality compared to normal weight, confirming the existence of the obesity paradox in this cardiac condition. No significant differences in hospitalization for heart failure during follow-up were observed between patients with normal weight, overweight and obesity.

Association between right ventricular remodeling and obesity in patients with significant TR

Significant TR is often associated with RV dilation and dysfunction due to volume overload of the RV (4). Accordingly, the RV size of the overall population in the current study was larger compared to reference values of healthy study populations (11, 16, 17). Obesity may also impact RV structure and function by a multifactorial mechanism of increased RV afterload, increased circulating blood volume, metabolic and neuroendocrine influences, and direct obesity-related myocardial effects (2, 18). The additional impact of obesity on RV dilation and dysfunction in patients with significant TR has not previously been investigated.

Most studies to date investigated RV size in obesity without cardiovascular comorbidities using cardiovascular magnetic resonance imaging (CMR) (19-21). Foppa et al. (19) demonstrated in 1794 participants of the Framingham Heart study that increased BMI was associated with larger RV end-diastolic volume indexed for height in both men and women. In contrast, in 739 subjects without cardiovascular risk factors, women displayed increased RV end-diastolic volume per BMI point increase, while in men no association between RV end-diastolic volume and BMI was demonstrated (20). The MESA-Right Ventricle Study by Chahal et al. (21) is the largest study to date evaluating the association between BMI and RV dimensions. In 4127 individuals without clinical heart disease, overweight and obesity were independently associated with greater RV end-diastolic volume on CMR, even after adjustment for respective LV parameters. Studies using echocardiography to assess RV size in obese individuals are scarce. The only published data

comparing RV end-diastolic area measured by 2-dimensional echocardiography across various BMI categories in a healthy population originates from a sub-study of the ARIC trial by Bello et al. (3), which demonstrated a significantly larger RV end-diastolic area with increasing BMI. Tadic et al. (22) reported similar results for indexed RV volumes measured by 3-dimensional echocardiography in 127 patients with untreated hypertension.

The current study extends these findings by demonstrating the additive effect of overweight and obesity on RV dilation in both men and women with significant TR. Similar to the results presented by Chahal et al. (21) changes in RV size were more pronounced than changes in LV size, suggesting that RV dilation is more than a generalized cardiac adaptation to a larger body size in obese patients. In our population, this difference could be explained by the additional impact of TR on volume overload of the thin walled RV, which is already more susceptible to dilation than the LV.

Despite the association between RV remodeling and obesity, RV systolic function as measured by TAPSE and RV fractional area change was not more impaired in patients with increasing BMI in our data. However, when using speckle tracking echocardiography to assess RV free wall strain, we observed more impaired RV systolic function in patients with larger BMI. Previous studies on the influence of BMI on RV function in different patient populations have yielded conflicting results. Interestingly, the studies that reported RV dilation in individuals without structural heart disease as discussed previously, also reported a significant reduction in RV systolic function in higher BMI groups (3, 21, 22). Likewise, Wong et al. (23) demonstrated a reduction of RV free wall strain in overweight and obese subjects compared to normal weight subjects without overt heart disease. In contrast, 153 obese participants of the Obesity Weight Reduction and Remodeling Study had similar TAPSE as age and gender matched healthy controls (24). Additionally, Takiguchi et al. (25) reported no significant differences in RV fractional area change between all BMI groups in a population of 648 patients hospitalized for decompensated heart failure. In the context of acute myocardial infarction, obese patients even had a better RV function measured by TAPSE than non-obese patients (26). The heterogenous results of these studies may be explained by factors that were not accounted for, such as duration of obesity, or by differences between study populations. In our population, the enhanced RV dilation in obese patients may be an initial adaptive response to increased circulating blood volume in order to preserve RV function by the Frank Starling mechanism. As this mechanism may become maladaptive over time, prospective trials with systematic RV function analysis during follow-up are needed to elucidate if targeting obesity could prevent or reverse RV remodeling and dysfunction.

Association of prognosis and obesity in patients with significant TR

Obesity is associated with the development of various cardiovascular diseases due to hemodynamic, metabolic and neuroendocrine effects of adipose tissue that lead to an unfavorable profile (1). Concordant with these mechanisms, overweight and obese patients in our population had a higher prevalence of obesity-related comorbidities (hypercholesterolemia, diabetes mellitus) and larger left and right atrial and ventricular volumes and areas. Notwithstanding, the current study demonstrated a better long-term survival in overweight and obese patients compared to normal weight patients with significant TR. This 'obesity paradox' for mortality has been described in various patient populations, but the mechanism remains unclear (7, 27, 28). Investigators have suggested several hypotheses, such as the production of protective cytokines by the adipose tissue (29). Moreover, obese patients may have a greater metabolic reserve or could become symptomatic at less severe stages of heart failure, and thus present earlier (29). Others suggested that the prognosis might be impacted by unmeasured confounding factors, as non-purposeful weight loss, leading to worse survival in patients with a lower BMI (29, 30). Banack et al. (31) suggested that the obesity paradox in cardiovascular diseases may be entirely explained by collider stratification bias (a correlation between an exposure and an unmeasured confounder due to selection on a third variable [collider] that is caused by both, which induces a false association between the exposure and outcome in case the confounder also influences the outcome). However, in the current population of patients with significant TR, the role of collider bias is uncertain. Firstly, collider bias can only occur if obesity causes TR. Although obesity is known to increase the risk for cardiovascular diseases as myocardial infarction, hypertension and atrial fibrillation, there is no evidence that obesity causes TR. In subjects of the Framingham Heart Study (32) the severity and prevalence of TR even decreased as a function of increasing BMI. This reverse association makes the hypothesis unlikely that obesity causes TR. However, despite lacking evidence, one may argue that obesity can cause TR by the pathophysiological mechanism of volume overload which leads to RV dilation and tricuspid annulus dilation, thereby causing secondary TR. Assuming obesity does cause TR, collider bias is still not the only explanation for the obesity paradox. As demonstrated by Sperrin et al. (33), for obesity as collider to reverse the harmful effect, the unmeasured confounders must have a very strong effect on TR and mortality. It is unlikely that confounders with such a strong association with TR and mortality are still unknown to the current medical world and therefore not included in the analysis. Consequently, a true physiologic protective effect of obesity on mortality in patients with significant TR is more plausible. Preclinical trials, clinical studies and bias analyses might further elucidate the mechanisms for the obesity paradox.

Interestingly, in the current population of patients with significant TR, higher BMI was not associated with a higher risk for heart failure hospitalization during follow-up, but was independently associated with a lower risk for the combined endpoint of all-cause mortality and heart failure hospitalization. This in contrast to the increased risk of heart failure in overweight and obese subjects as demonstrated in 5,881 participants of the Framingham Heart Study (1). These contrasting results suggest that even though obesity is a risk factor for heart failure in healthy populations, a higher BMI in the presence of established cardiovascular disease like significant TR, is associated with a lower risk for heart failure hospitalization, confirming the presumption of an obesity paradox for heart failure as well.

To the best of our knowledge, the current study is the first to demonstrate the independent association between obesity and prognosis in patients with significant TR. These counterintuitive findings emphasize the need for further studies to confirm our results. Better understanding of the favorable phenotype of obese patients and the mechanism behind the obesity paradox may help clinicians in applying risk-reducing treatment in this patient population.

Study limitations

The current study is subject to limitations inherent to the retrospective and single center design. No information was available on physical activity, the duration of obesity, the distribution of adipose tissue and weight loss, all of which could influence RV remodeling and prognosis (7, 21). BMI, even though it is a surrogate for true body adiposity, is highly correlated to anthropometric measures of body fat (3, 21) and is an easy to use parameter for caregivers in risk stratification.

The presence of obstructive sleep apnea was not documented, even though this disease is associated with obesity and may increase afterload of the RV and thereby enhance RV remodeling due to pulmonary arterial hypertension (34). However, Wong et al. (23) found no relationship between sleep apnea severity and RV characteristics. Furthermore, pulmonary pressures were assessed in our study and did not differ significantly across BMI groups.

No healthy controls were included in the current study. To assess the impact of significant TR and obesity on RV remodeling compared to normal subjects, reference values of RV measurements in healthy subjects from the largest studies to date were used (3, 11, 16, 17). However, data on RV size are challenging to compare because data are inconsistently presented with and without indexation for BSA or height. Current recommendations

differentiate normal values for men and women, but do not specify different normal ranges for higher BMI groups (11). We chose to index RV parameters for height to correct for a generalized cardiac adaptation to a larger body size, but to prevent overcorrection for the effects of obesity. After correction for height, RV size was similar in both sexes in the current study. Explicit guidelines on how to present reference values on RV size could improve comparability across studies.

Measuring RV function by two-dimensional echocardiography is challenging. Given the higher blood volume and compensatory mechanisms that initially lead to increased stroke volume in obese patients, load dependent measurements as TAPSE are not ideal to assess RV systolic function in patients with higher BMI. However, TAPSE is the most validated method and most used in clinical practice (14). Furthermore, similar results were observed with RV fractional area change. Longitudinal data from sequential echocardiograms over time were not analyzed since the data were not gathered systematically (only at the discretion of the treating physician) and may introduce a significant bias.

Conclusion

In a large cohort of patients with moderate and severe TR, overweight and obesity were associated with more pronounced RV dilation compared to normal weight patients. This RV remodeling appears to be adaptive, since no significant differences across BMI groups were observed in RV systolic function. Additionally, higher BMI was independently associated with better survival during long term follow-up, supporting the concept of the 'obesity paradox' being applicable to patients with significant TR.

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Supplemental Table 1. The association between RV end-diastolic area in patients with normal weight, overweight and obesity according to quantitatively assessed TR grades

	Overall (n=852)	EROA<20 (n=44)	EROA 20-39 (n=125)	EROA≥40 (n=683)	P-value
RV end-diastolic area/height, cm^2/m	13 (11-17)	14 (10-17)	12 (10-15)	14 (11-17)	**0.001**
RVEDA/ht in normal weight	13 (10-16)	14 (10-16)	12 (9-14)	13 (11-16)	**0.038**
RVEDA/ht in overweight	14 (11-17)	13 (10-16)	13 (11-17)	14 (11-17)	0.335
RVEDA/ht in obese	15 (12-18)	17 (10-17)	12 (10-12)	15 (12-19)	**0.004**
P-value	**<0.001**	0.719	**0.046**	**<0.001**	

Values are median (IQR).

EROA = effective regurgitant orifice area; ht = height; RV = right ventricular; RVEDA = right ventricular end-diastolic area

Supplemental Table 2. Univariable and multivariable Cox proportional hazard models for the combined endpoint of hospital admissions for heart failure and all-cause mortality in patients with tricuspid regurgitation with BMI in categories (model 1) and BMI as continuous variable (Model 2)

Variable	Univariate analysis		Multivariate analysis – Model 1		Multivariate analysis – Model 2	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age	1.012 (1.004-1.020)	**0.002**	1.015 (1.006-1.023)	**0.001**	1.014 (1.006-1.023)	**0.001**
Male sex	1.341 (1.105-1.627)	**0.003**	1.034 (0.828-1.290)	0.770	1.015 (0.813-1.267)	0.894
Diabetes mellitus	1.655 (1.305-2.098)	**<0.001**	1.234 (0.934-1.629)	0.138	1.255 (0.951-1.655)	0.108
Hypercholesterolemia	1.225 (1.006-1.493)	**0.044**	0.923 (0.741-1.149)	0.472	0.919 (0.738-1.145)	0.452
Creatinine	1.003 (1.003-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**	1.003 (1.002-1.004)	**<0.001**
Diuretics	2.134 (1.733-2.629)	**<0.001**	1.613 (1.274-2.041)	**<0.001**	1.599 (1.262-2.025)	**<0.001**
LV end-diastolic volume/ht	1.008 (1.006-1.010)	**<0.001**	1.006 (1.004-1.008)	**<0.001**	1.006 (1.004-1.008)	**<0.001**
LV ejection fraction	0.980 (0.974-0.987)	**<0.001**	0.993 (0.986-1.001)	0.088	0.994 (0.982-1.001)	0.103
E/A ratio	1.004 (0.989-1.020)	0.582				
TA diameter/ht	1.031 (1.008-1.054)	**0.008**	1.006 (0.981-1.031)	0.657	1.007 (0.982-1.032)	0.586
RV end-diastolic area/ht	1.010 (1.003-1.017)	**0.004**	1.003 (0.994-1.014)	0.574	1.002 (0.994-1.011)	0.610
TAPSE	0.953 (0.934-0.973)	**<0.001**	0.977 (0.955-0.999)	**0.037**	0.978 (0.957-1.000)	0.052
RV free wall longitudinal strain (each 1% decrease)	1.039 (1.023-1.055)	**<0.001**				
Severe TR	1.140 (0.902-1.442)	0.272				
BMI groups		0.097		**0.005**	----------	-------
Normal weight (reference)	----------	-------	----------	-------	----------	-------
Overweight	0.830 (0.674-1.022)	0.079	0.714 (0.571-0.893)	**0.003**	----------	-------
Obese	0.763 (0.557-1.046)	0.093	0.683 (0.481-0.971)	**0.033**	----------	-------
BMI (continuous)	0.968 (0.943-0.994)	**0.016**	----------	-------	0.952 (0.923-0.981)	**0.002**

BMI = body mass index; CI = confidence interval; E/A = ratio of mitral inflow peak early diastolic flow velocity to atrial contraction peak velocity; ht = height LV = left ventricular; RV = right ventricular; TA = tricuspid annulus; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation