

Successful Weight Reduction Improves Left Ventricular Diastolic Function and Physical Performance in Severe Obesity

Sabine FENK,¹ MD, Marcus FISCHER,¹ MD, Christina STRACK,¹ MD, Gerd SCHMITZ,² MD, Thomas LOEW,¹ MD, Claas LAHMANN,³ MD, and Andrea BAESSLER,¹ MD

SUMMARY

Obesity and the metabolic syndrome (MetS) are risk factors for left ventricular diastolic dysfunction (LVDD). However, little is known about the impact of successful weight reduction (WR) on diastolic function and physical performance.

Obese subjects ($\bar{\text{BMI}} 40.2 \pm 8.6 \text{ kg/m}^2$) underwent a 1-year WR program comprising diet and lifestyle components. Echocardiography and exercise capacity (6-minute walk) were performed at baseline and after 1 year. The distribution of weight reduction was split at the sample median and subjects were dichotomized in “successful WR” (% WR \geq median, corresponding to a weight loss of 8%) and “failed-WR” (% WR < median).

From a total of 188 obese subjects, 71 had LVDD at baseline. Obese patients with successful WR improved their MetS alterations, including fasting glucose, insulin, lipids, adipokines, blood pressure levels, and epicardial fat thickness. The same was not true for obesity with failed WR. Subjects with successful WR demonstrated significant improvement in echocardiographic LVDD parameters (median [interquartile range]): $\Delta e'$ (2.5 [-1.0, 4.7], $P < 0.01$), $\Delta e'/a'$ (0.34 [0.07, 0.79], $P < 0.01$), $\Delta E/e'$ (-1.14 [-2.72, -0.54], $P < 0.05$), $\Delta E/A$ (0.08 [-0.04, 0.26], $P < 0.05$), $\Delta \text{Ard-Ad}$ (-28 [-54, -4], $P < 0.01$), and 6-minute walk distance (65 [19, 135], $P < 0.01$). Improvement of ≥ 2 LVDD criteria was accomplished in 30% of subjects with WR versus 10% without ($P = 0.009$). Using multivariable regression analysis, reduction of epicardial fat thickness was particularly predictive for the improvement of diastolic function.

In summary, in severe obesity, successful long-term WR was associated with improved LV diastolic function and exercise capacity. (Int Heart J 2015; 56: 000-000)

Key words: Adiposity, Metabolic syndrome, Diastolic dysfunction, Weight loss

Obesity and metabolic syndrome (MetS) are increasing in global prevalence. Accompanying these trends there is a concerning shift in the population weight distribution toward the more extreme ends of obesity, given an increased risk for cardiovascular morbidity and mortality that is associated with excess adiposity.¹⁻⁴⁾ One associated finding is an impairment of cardiac performance leading to myocardial systolic and diastolic dysfunction and clinical symptoms often indistinguishable from heart failure. In fact, evidence of left ventricular diastolic dysfunction (LVDD) is a common finding in the obese, and consequently, obesity is considered a risk factor for diastolic heart failure.⁵⁻⁹⁾

Although lifestyle modification and weight reduction are routinely recommended to improve symptoms and to reduce cardiovascular risk in the obese with metabolic disorders, their effects on diastolic function and physical performance have been studied only rudimentarily, particularly in adults with severe obesity. Thus, the aim of the present study was to assess

the effect of long-term lifestyle and weight reduction programs on these measures in severely obese subjects with varying degrees of MetS.

Notably, there is considerable variation in biological determinants, encompassing metabolic and endocrine factors and in the degree of weight loss per se achieved by individuals in response to caloric restriction and physical activity.^{10,11)} In this regard, it is of interest that several of these biological determinants may independently influence diastolic function or modify the effect of weight loss on hemodynamics and cardiovascular function. Thus, given an improvement of diastolic function by successful weight reduction, a further aim of this study was to characterize the relative contributions of various improved metabolic and physiological parameters, induced by weight reduction, on diastolic function.

From the ¹ Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, ² Institut für Klinische Chemie und Laboratoriumsmedizin, Universitätsklinikum Regensburg, Regensburg, and ³ Klinik für Psychosomatische Medizin, Technische Universität München, Munich Germany.

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Address for Correspondence: Andrea Baessler, MD or Marcus Fischer, MD, Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg Franz-Josef-Strauß-Allee 11, D-93053 Regensburg, Germany. E-mail: andrea.baessler@ukr.de or marcus.fischer@ukr.de

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METHODS

Study population: Subjects were participants of the “Obesity Weight Reduction and Remodeling Study”, an ongoing 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 intending to participate in a weight reduction program are offered enrollment in this study prior to the start of the program. Patients are eligible for enrollment if they participate 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, or in a combined exercise and diet weight reduction program offered by a local fitness gym. However, for the present study, only subjects who followed a hypocaloric diet were considered. Patients were eligible 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 they signed a declaration of consent. Patients were excluded if they had one or more of the following: 10% reduction of body weight in the last 6 months, cancer, pregnancy, therapy with steroids or thyroid hormones, known heart disease, known type 1 or type 2 diabetes, known inflammatory bowel, rheumatoid, or systemic diseases, known chronic renal failure, known liver diseases, history of psychiatric illness, or addiction to drugs or alcohol. The study was approved by the local Ethics Committee.

Follow-up and definition of successful weight reduction: Anthropometric examinations were conducted at baseline, after 3 months (reduced phenotyping protocol), and at the end of the program (after 1 year). The distribution of weight reduction was split at the sample median and subjects were dichotomized into successful WR (“WR”, when % WR ≥ median) and “failed-WR” (when % WR < median). In the total “Obesity Weight Reduction and Remodeling Study” (including the Optifast-52 and local fitness gym programs) the median weight loss after 1 year was 8% of baseline weight. Consequently, in the present study sample successful WR was a weight loss of at least 8% of baseline weight. The time courses of weight change in subjects with successful and failed weight reduction are demonstrated in Supplemental Figure 1. Weight reduction was more pronounced and stable in subjects with successful WR compared to subjects with failed WR. Identical time courses appeared for subjects stratified according to baseline LVDD (data not shown).

Echocardiography: Echocardiography was performed at baseline and at the end of the program using a standard ultrasound system (Philips iE33 Philips Medical Systems, Hamburg, Germany). Details of the thorough echocardiographic examination and measurements were described before.¹²⁾ Epicardial fat was identified as the space or layer anterior to the right ventricle with decreased echoreflexivity compared with the myocardium and pericardium. Epicardial fat thickness was measured in end-diastole on the free wall of the right ventricle from the parasternal long-axis (Supplemental Figure 2) and short-axis views, according to the method previously described and validated by Iacobellis and Willens.¹³⁾ The concordance correlation coefficient, a measure of precision and accuracy,¹⁴⁾ for 20 duplicate measurements of two expert echocardiographers was 0.87 ± 0.11 ($P < 0.001$) indicating good interobserv-

er agreement. The cardiologists who performed the echocardiograms were blinded to the time of investigation (baseline or 12-months follow-up investigation) and to knowledge about whether the subject lost weight. With respect to Doppler measurements, the concordance correlation coefficient for 20 duplicate E/e' measurements of the two echocardiographers was 0.97 ± 0.02 ($P < 0.0001$) indicating high reproducibility of these Doppler parameters.

Definition of diastolic dysfunction: Diastolic dysfunction was defined if the following criteria were fulfilled: 1) a preserved systolic LV function (EF > 50%); and 2) presence of at least two of the following criteria consistent with abnormal left ventricular relaxation, filling, diastolic distensibility, or diastolic stiffness⁵⁾: E/e' lat. > 8, E/A < 0.8 and deceleration time (DT) > 200 ms or E/A > 2 and DT < 160 ms, e' lat. < 10 cm/s, e'/a' < 0.9, S (systolic) < D (diastolic) pulmonary venous flow, difference in duration of pulmonary venous and mitral flow at atrial contraction (Ard-Ad) > 0 ms, LV-mass > 149 g/m² (in men), > 122 g/m² (in women), or an enlarged left atrial (LA)-size (LA area (4 CH planimetry) > 20 cm² or LA diameter (PLAX) > 48 mm). In contrast, subjects with a normal lateral e' ≥ 10 cm/s together with a normal LA-size were classified as having normal LV-function according to ASE 2009 consensus criteria.¹⁵⁾

Definition of metabolic syndrome: MetS was diagnosed according to the NCEP Adult Treatment Panel III (ATPIII). It requires the presence of central obesity with waist circumference ≥ 102 cm in men and ≥ 88 cm in women, dyslipidemia with triglycerides ≥ 150 mg/dL, and HDL-cholesterol < 40mg/dL in men and < 50 mg/dL in women.

Hypertension and hyperglycemia were diagnosed for blood pressure ≥ 130/85 mmHg and fasting plasma glucose ≥ 110 mg/dL. MetS was diagnosed when at least 3 out of 5 metabolic abnormalities were determined.

Physical performance: Patients performed the 6-minute walk test at study entry and at the end of the program at 1 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 read using an electronic meter counter, and the maximum heart rate was immediately measured.

Biochemical and anthropometric phenotyping: All subjects were studied after a 12 hour overnight fast between 7:00 and 9:00 am in standardized fashion. All anthropometric measurements were performed by specially trained staff using standard techniques. Blood pressure (BP) and heart rate were taken after a sitting period of 5 minutes. We measured blood pressure 3 times on both arms with an appropriate sized blood pressure cuff with at least 60 seconds between the measurements.

Height and weight were recorded with participants wearing lightweight clothing and no shoes using a centimetre scale with attached stadiometer.

Body composition was determined by bioelectrical impedance analysis (BIA) using a Nutriguard©-Impedance Analysis Apparatus (Data Input GmbH Darmstadt, Germany). The fat mass index (FATI) was calculated as the ratio fat mass/height squared. Routine blood parameters were immediately measured at the Institute of Clinical Chemistry and Laboratory Medicine of University Hospital of Regensburg. Plasma samples were sampled and stored at -70°C for the more laborious enzyme-linked immunosorbent assays. For these measure-

ments, the samples had not been thawed before. GDF-15 concentrations were determined by enzyme-linked immunosorbent assay (Quantikine, R&D Systems Europe, Wiesbaden, Germany). NT-proBNP levels were determined by a standard chemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

Statistical analysis: Categorical variables were compared using the likelihood ratio test. Continuous variables of baseline data are reported as the mean and its standard deviation. Normally distributed variables were compared using one-way analysis of variance and non-normally distributed variables were compared using the Kruskal–Wallis test. The deltas (follow-up minus baseline data) are reported as medians with interquartile range due to skewed distributions. With respect to longitudinal studies, the nonparametric Wilcoxon signed rank test was used for the analysis of repeated measures (between pairs of values before and after weight reduction).

In addition, the continuously distributed percent changes of diastolic function variables after 12 months were also converted into a dichotomous variable by splitting the data into “improved” (improvement in diastolic function parameters of at least 25%) and “not improved” (improvement below 25%). The cut-off level of 25% corresponds to the upper 95% confidence interval of the percent change in e' in $n = 54$ age-matched and sex-matched healthy normal weight control subjects who were also examined in 12-month time intervals. Contingency analysis was then used to compare the proportion of improved/non-improved subjects in association with successful/failed weight reduction by means of the likelihood ratio test. Multiple linear regression was performed to analyze the independent effects of several cardiometabolic variables associated with weight reduction on parameters of left ventricular diastolic function adjusted for age and sex. Variables found to be significant by univariate analysis were entered into stepwise multivariable models, with the criterion of $P < 0.25$ for a variable to enter and $P < 0.10$ to stay in the model.

Because most cardiometabolic variables are intercorrelated and, in part, strongly influenced by weight reduction (resulting in multicollinearity) it would be uncertain whether weight reduction by itself or other cardiovascular or metabolic improvements predict changes in diastolic function. Thus, in order to quantify an individual regressor's contribution to multiple regression analysis, variable importance statistics were performed. Here, standardized beta weights were calculated for each given independent variable and were interpreted as the expected difference in the dependent variable score between people who differ by one standard-deviation unit on that independent variable, with all other independent variable scores held constant. Moreover, because shared variance between independent variables impacts upon the regression equation, commonality analysis was used to determine how much variance an independent variable contributes to the regression equation that is not shared with other independent variable (squared semipartial correlations).¹⁶⁾ Statistical significance was considered at the 0.05 level. All analyses were conducted using JMP Version 9 (SAS Institute Inc., Cary, NC, USA) and STATA 8 (Statacorp., College Station, TX, USA).

RESULTS

From a total of 188 obese patients, 79 achieved successful weight reduction (WR) while 109 did not (failed WR). LVDD was present in 71 obese patients, and 34 of them achieved successful WR.

Clinical and laboratory characteristics at baseline: Baseline clinical characteristics are displayed in Table I. Obese subjects with LVDD were significantly older, and had a more pronounced metabolic risk profile such as higher BMI, larger waist circumference, higher blood pressure levels, and higher fasting glucose, insulin, HDL cholesterol, and leptin levels in comparison to obese subjects with no LVDD at baseline. Concerning potential heart failure parameters, obese with LVDD presented with higher GDF-15 levels and reached a significantly shorter 6-minute walk distance than obese with normal LV function. Subjects with successful weight reduction were largely comparable to subjects with failed weight reduction at baseline.

Echocardiographic characteristics at baseline: Echocardiographic characteristics were broadly similar in LVDD obese with failed and successful WR at baseline and are shown in Table II. By definition, obese subjects with LVDD presented with higher septal and relative wall thickness, and lower e' and e'/a' ratios, as well as a higher LV end-diastolic filling index E/e' . Moreover, obese with LVDD had a higher LV-mass, a larger left atrium, and a higher epicardial fat thickness.

Clinical characteristics at follow-up: At 1-year follow-up subjects with successful weight loss had a median reduction in BMI of 6.8 kg/m^2 ($P < 0.01$ versus baseline) compared to those who did not achieve the target weight loss goal of at least 8% ($+0.1 \text{ kg/m}^2$). Accordingly, all parameters of body composition were significantly improved in subjects with successful WR (Supplemental Table I).

Importantly, successful WR was accompanied by several cardiometabolic improvements, encompassing decreases in both systolic and diastolic blood pressure, and reductions of fasting glucose, insulin, HOMA-IR, and triglyceride levels. Moreover, successful weight loss was associated with significant changes in adipokines, as well as potential heart failure markers such as GDF-15 and MMP-9. These findings were especially observed in the group of LVDD obese.

Whereas 6-minute walk distance at baseline was similar in both groups with and without successful WR, a significant gain in the achieved 6-minute walk distance could only be observed in the group with effective WR, and was more pronounced in the group with baseline LVDD (65 m, interquartile range 19–138 m, $P < 0.0001$ versus baseline). In parallel, peak heart rate was reduced in obese with successful WR. Moreover, after participation in the weight reduction program we found significant correlation between the changes in echocardiographic diastolic function parameters and change in 6-minute walk distance (ie, correlation of $\Delta e'$ -velocity with Δ 6-minute walk distance, $r = 0.33$, $P < 0.001$, data not shown).

Echocardiographic characteristics at follow-up: Echocardiographic results at 1-year follow-up are shown in Table III. Obese with LVDD achieving successful long-term WR demonstrated a significant improvement in echocardiographic parameters of LVDD, including $\Delta E/A$, $\Delta e'$, $\Delta e'/a'$, ΔArd , and $\Delta \text{Ard-Ad}$. In addition, the “filling index” E/e' decreased signif-

Table I. Baseline Characteristics of Obese Study Participants With and Without Successful Weight Reduction (WR) and LV Diastolic Dysfunction (LVDD)

	No-LVDD obese		LVDD obese		Level of significance (No-LVDD versus LVDD obese)
	Failed WR (n = 72)	WR (n = 45)	Failed WR (n = 37)	WR (n = 34)	
Sex (% female)	59	41	52	41	NS
Age (years)	42 ± 12	40 ± 12	49 ± 12	51 ± 10	< 0.01
BMI (kg/m ²)	36.2 ± 7.3	40.4 ± 9.3 [†]	41.1 ± 9.7	42.7 ± 9.4	< 0.01
Waist (cm)	107 ± 18	120 ± 19 [†]	122 ± 18	129 ± 20	< 0.05
FATI (kg/m ²)	15.6 ± 4.8	17.4 ± 4.7 [†]	18.4 ± 8.2	18.0 ± 6.7	< 0.01
Syst. BP (mmHg)	133 ± 13	138 ± 16	142 ± 18	144 ± 19	< 0.01
Diast. BP (mmHg)	83 ± 10	87 ± 13	88 ± 12	89 ± 13	< 0.05
Hypertension (%)	31	51 [*]	60	55	< 0.05
HR (bpm)	73 ± 13	76 ± 11	70 ± 14	76 ± 14 [*]	NS
Glucose (mg/dL)	92 ± 21	97 ± 26	98 ± 24	113 ± 41 [*]	< 0.01
Insulin (U/mL)	17 ± 17	23 ± 18	23 ± 19	27 ± 21	< 0.05
HOMA-IR	4.4 ± 7.9	5.9 ± 6.0	6.1 ± 6.4	8.1 ± 9.6	< 0.05
T2DM (%)	4	7	5	16	NS
MetS (%)	35	53	48	61	NS
Triglycerides (mg/dL)	120 ± 59	133 ± 69	142 ± 60	153 ± 92	< 0.05
Adiponectin (μg/mL)	9.3 ± 3.9	9.5 ± 3.6	8.7 ± 4.1	9.0 ± 4.6	NS
HDL-Chol. (mg/dL)	54 ± 19	52 ± 15	47 ± 11	46 ± 12	< 0.05
Leptin (μg/L)	56 ± 79	60 ± 8	51 ± 46	49 ± 31	< 0.05
hsCRP (mg/L)	6.0 ± 6.0	8.8 ± 11.2	7.8 ± 8.7	6.1 ± 4.8	NS
TNF-α (pg/mL)	9.3 ± 2.6	9.7 ± 5.0	10.6 ± 2.8	10.2 ± 4.3	NS
NTproBNP (ng/L)	61 ± 51	67 ± 70	86 ± 117	118 ± 201	NS
GDF15 (pg/mL)	602 ± 251	587 ± 332	694 ± 269	779 ± 377	< 0.01
MMP9 (ng/mL)	583 ± 300	635 ± 248	743 ± 360	690 ± 392	< 0.05
6-minute walk (m)	574 ± 80	584 ± 78	541 ± 155	540 ± 101	< 0.01
peak HR (bpm)	124 ± 24	124 ± 26	108 ± 26	118 ± 24	< 0.01

Weight reduction (WR) was defined as ≥ 8% (sample median) weight loss. BMI indicates body mass index; BP, blood pressure; bpm, beats per minute, FATI, fat mass/height²; HOMA-IR, homeostasis model assessment insulin resistance; HR, heart rate; MetS, metabolic syndrome; and T2DM, diabetes mellitus type II. ^{*}P < 0.05, [†]P < 0.01 'Failed WR' versus 'WR'.

Table II. Baseline Echocardiographic Characteristics of Obese Study Participants With and Without Successful Weight Reduction (WR) and LV Diastolic Dysfunction (LVDD)

	No-LVDD obese		LVDD obese		Level of significance (No-LVDD versus LVDD obese)
	Failed WR (n = 72)	WR (n = 45)	Failed WR (n = 37)	WR (n = 34)	
IVS (mm)	9.2 ± 1.6	10.2 ± 1.5	11.9 ± 1.9	12.0 ± 2.2	< 0.01
RWT	0.37 ± 0.07	0.38 ± 0.05	0.42 ± 0.06	0.42 ± 0.07	< 0.01
LVEDD (mm)	49 ± 9	51 ± 5	53 ± 5	53 ± 9	NS
LVESD (mm)	30 ± 7	31 ± 4	34 ± 5	33 ± 7	NS
EF (%)	65 ± 6	66 ± 6	64 ± 7	63 ± 9	NS
E/A	1.2 ± 0.3	1.2 ± 0.4	1.1 ± 0.4	1.1 ± 0.5	< 0.05
DT (ms)	203 ± 62	196 ± 47	220 ± 69	233 ± 86	< 0.05
IVRT (ms)	94 ± 24	95 ± 16	108 ± 14	105 ± 21	< 0.05
e' (cm/s)	15.0 ± 5.0	14.7 ± 3.3	9.9 ± 3.0	10.4 ± 5.7	< 0.01
e'/a'	1.5 ± 0.6	1.4 ± 0.5	1.0 ± 0.5	0.9 ± 0.5	< 0.01
E/e'	5.9 ± 1.5	6.0 ± 1.1	8.5 ± 2.5	8.0 ± 2.7	< 0.01
S/D ratio	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	NS
Ard (ms)	131 ± 31	136 ± 35	151 ± 42	155 ± 61	< 0.01
Ard - Ad (ms)	-30 ± 46	-21 ± 33	-14 ± 46	-13 ± 51	< 0.05
LV mass _{BSA} (g/m ²)	104 ± 19	104 ± 21	133 ± 30	138 ± 32	< 0.01
LV mass (g)	235 ± 69	249 ± 78	325 ± 89	345 ± 98	< 0.01
LA area (cm ²)	16.9 ± 1.9	18.4 ± 4.1	22.0 ± 4.2	22.0 ± 5.0	< 0.01
Epicard. Fat (mm)	5.3 ± 2.6	6.4 ± 3.4 [*]	8.0 ± 3.3	8.0 ± 3.6	< 0.01

Weight reduction (WR) was defined as ≥ 8% (sample median) weight loss; ^{*}P < 0.05, [†]P < 0.01 'Failed WR' versus 'WR'. IVS indicates interventricular septum; RWT, relative wall thickness; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; E/A, ratio E velocity/A velocity; EF, ejection fraction; DT, deceleration time; IVRT, isovolumic relaxation time; e', early diastolic velocity; e'/a', ratio early diastolic velocity/late diastolic velocity; S/D ratio, ratio peak systolic velocity/peak diastolic velocity; Ard, duration of atrial reverse velocity; Ard - Ad, difference duration of Ar and duration of A (Ad); LV, left ventricle; and LA, left atrium.

Table III. Deltas (Follow-up – Baseline Data) of Echocardiographic Characteristics of Obese Study Participants With and Without Successful Weight Reduction (WR) and Diastolic Dysfunction (LVDD)

	No-LVDD obese		LVDD obese	
	Failed WR (n = 72)	WR (n = 45)	Failed WR (n = 37)	WR (n = 34)
Δ IVS (mm)	0 (-1, 1)	0 (-1, 1)	0 (-1, 0)	0 (-1, 0)
Δ RWT (%)	0.01 (-0.03, 0.06)	0.01 (-0.01, 0.05)	0 (-0.03, 0.04)	-0.01 (-0.05, 0.02)
Δ LVEDD (mm)	-1 (-2, 3)	0 (-3, 4)	0 (-1, 1)	0 (-3, 2)
Δ LVESD (mm)	0 (-2, 2)	0 (-1, 2)	0 (-2, 1)	0 (-2, 2)
Δ EF (%)	2.0 (-3.0, 7.0)	0 (-3.5, 5.0)	-1.0 (-5.5, 5.5)	0.4 (-6.0, 3.0)
Δ DT (ms)	-3 (-53, 30)	-11 (-49, 39)	-21 (-95, 25)	-19 (-89, 44)
Δ IVRT (ms)	3 (-16, 23)	-1 (-15, 17)	-7 (-21, 0)	-3 (-19, 20)
Δ E/A	-0.03 (-0.2, 0.1)	0.06 (-0.16, 0.28)	-0.07 (-0.2, 0.06)	0.08 (-0.04, 0.26)*
Δ e' (cm/s)	-1.7 (-4.5, 0.7)	0.7 (-1.7, 2.4)	0.2 (-2.4, 1.8)	2.5 (-1.0, 4.7)†
Δ e'/a'	-0.07 (-0.43, 0.28)	0.17 (-0.04, 0.50)	-0.08 (-0.24, 0.27)	0.34 (0.07, 0.79)†
Δ E/e'	0.46 (-0.80, 2.66)	-0.23 (-1.17, 1.32)	-0.18 (-1.39, 2.14)	-1.14 (-2.72, 0.54)†
Δ Ard (ms)	-7 (-30, 6)	-13 (-39, 18)	-21 (-42, 10)†	-28 (-44, -2)†
Δ Ard – Ad (ms)	0 (-28, 21)	-18 (-46, 5)	-18 (-56, 2)*	-28 (-54, -4)†
Δ LVmass (g)	0.9 (-25.2, 28.8)	-7.6 (-40.0, 27.7)	-8.5 (-19.6, 12.3)	-20.0 (-60.5, 24.7)*
Δ S/D ratio	-0.06 (-0.19, 0.19)	-0.02 (-0.17, 0.17)	-0.07 (-0.25, 0.12)	0.01 (-0.25, 0.30)
Δ LA area (cm ²)	-0.1 (-1.5, 2.7)	0.5 (-1.7, 2.2)	-1.2 (-3.0, 1.4)	-0.7 (-2.5, 1.8)
Δ Epicard. Fat (mm)	-0.8 (-2.3, 0.6)	-2.2 (-3.3, -0.7)†	-0.9 (-3.3, 0.9)	-2.4 (-5.6, -0.4)†

Data are presented as median and interquartile range in parentheses. * $P < 0.05$, † $P < 0.01$ versus baseline data.

icantly in the group of obese with LVDD with successful WR. Moreover, parameters of left ventricular geometry and size were decreased significantly after effective weight reduction, namely LV mass and epicardial fat thickness. In contrast, the reduction in left atrial size was not statistically significant.

We compared the proportion of subjects demonstrating improvement in echocardiographic parameters and exercise capacity amongst those with failed and successful WR (Supplemental Figure 3). A significantly greater proportion of those with successful WR demonstrated improvement in dichotomized $\Delta E/A$, $\Delta e'$, $\Delta e'/a'$, $\Delta E/e'$, and $\Delta 6$ -minute walk distance. Furthermore, in comparison to those who failed to achieve target weight loss, more patients with successful WR demonstrated simultaneous improvements in at least two LVDD criteria.

Relative importance analysis in multiple linear regression: Supplemental Table II displays the results of multiple linear and logistic regression analysis after selecting the final model using a stepwise regression procedure. For various improvements in LVDD criteria the highest beta weights could be observed for change in epicardial fat thickness. Moreover, epicardial fat thickness was the only variable that has a statistically significant increment to R^2 , implying that reduction in epicardial fat rather than other metabolic improvements was the most important determinant for the improvement of diastolic functioning in this analysis.

DISCUSSION

Left ventricular diastolic dysfunction (LVDD) is a well-recognized consequence of obesity which can progressively lead to heart failure, and is linked to increased mortality.¹⁷⁻²⁰⁾

Since established systolic heart failure drug management revealed rather disappointing benefits in diastolic heart failure, it is important to investigate whether LVDD is potentially reversible by weight reduction, and to understand the mechanisms by which obesity interacts with LVDD. Our prospective

weight loss study reports the following findings: first, in agreement to earlier reports,²¹⁻²⁶⁾ severe obesity is related to several parameters of diastolic function. Second, there is evidence of improvement in diastolic function in those who achieved successful weight reduction and this is translated to a noticeable increase in exercise capacity. In addition, successful weight reduction in the severe obese goes along with several positive pleiotropic effects, such as reduction in blood pressure and heart rate, improved insulin/glucose metabolism, improved blood lipids, as well as ameliorated adipokines, corroborating previous findings on the beneficial effects of weight reduction on cardiovascular morbidity.²⁷⁻³⁰⁾

Since obesity is associated with cardiovascular risk factors such as hypertension and diabetes, as well as with cardiac structural changes such as CAD, obesity might be found as an indirect predictor for LVDD. Indeed, it has been recently reported that exercise and weight loss may improve exercise capacity due to a general improvement of MetS parameters but independently of cardiac function in obese subjects with the MetS.³¹⁾ In agreement with this study, we also observed marked improvements in several MetS parameters in subjects with successful weight loss, including blood pressure, insulin sensitivity, dyslipidemia, markers of oxidative stress and endothelial dysfunction, as well as adipokines. All of these determinants may independently influence diastolic function or modify the effect of weight loss on cardiovascular hemodynamics and functioning.

However, obesity may also be associated with structural changes in the myocardium independent of its effects on risk factors or CAD. In fact, changes in myocardial metabolism and fatty infiltration have been demonstrated in the obese which may affect cardiac structure and function.³²⁾ Moreover, obese individuals have increased total blood volume and volume load on the heart which creates a high cardiac output state, leading to left ventricular hypertrophy and, consequently, to LVDD.^{32,33)}

The close anatomical proximity of epicardial adipose tis-

sue to the adjacent myocardium also suggests possible local interactions.³⁴⁾ Epicardial adipose tissue is a metabolically active organ that generates various bioactive molecules, which might significantly affect cardiac function.³⁴⁾ Exemplarily, the adipocyte fatty acid-binding protein (FABP4) was recently identified as an adipokine that might directly depress cardiac contractile function.³⁵⁾

It could also be assumed that the increased epicardial fat mechanically affects left and right ventricular diastolic filling and consequently induces atrial enlargement. In this regard, epicardial fat volume has been described as an independent predictor of impaired diastolic function in otherwise healthy overweight patients.²⁶⁾ In our study, we observed a higher epicardial fat thickness in obese with LVDD and a significant reduction of epicardial fat thickness among subjects with successful weight reduction.

A special aim of this study was to characterize the relative contributions of various improved metabolic and physiological parameters, induced by weight reduction, on diastolic function. In our relative importance analysis using commonality analysis assessing the factors that affect diastolic function during the course of a long-term weight reduction program, we found that the reduction of epicardial fat thickness was particularly associated with the improvement of diastolic functioning during weight loss. However, as we measured only epicardial fat thickness, but not the exact epicardial fat volume, further studies are necessary to investigate the role of epicardial fat on cardiac structure and function in more detail. Likewise, as we have no direct measurements of visceral abdominal fat, we cannot discern what is more or less important for LVDD in the obese.

To our knowledge, clinical investigations evaluating the relation between weight reduction on diastolic function and its impact on physical fitness in the severe obese are lacking. So far several studies after bariatric surgery could show an improvement of diastolic function after successful weight reduction.³⁶⁻³⁹⁾ One found an increase in the E/A ratio in obese patients after gastric bypass 7 months after surgery.³⁹⁾ However, bariatric surgery is not a first line approach and risks of surgical procedures in obese patients should not be neglected. Foremost, guidelines recommend lifestyle intervention and exercise, therefore, it is important to assess responses to conventional non-surgical weight reduction regimens.⁴⁰⁾ In one study in obese subjects who had significant weight reduction after a lifestyle intervention program, an increase in e'-velocity, but no changes in E/A and E/e' ratios were reported.⁴¹⁾ Likewise, moderate short-term weight loss by lifestyle modification resulted in no significant alterations to either cardiac or vascular structure and function.⁴²⁾ This may have been related to the modest degree and/or short duration of weight loss. In our study, the weight reduction was sustained in the long-term up to one year. The heart may require time to adapt in response to change in physical or chemical conditions so longer-term follow up may be advantageous. Concordantly, Rider, *et al.* in 2012 reported beneficial effects after long-term weight loss on impaired cardiac energetics and myocardial relaxation in 13 obese subjects.⁴³⁾ Although the weight loss methodology varied and the study sample was small, this study suggested an improved myocardial phosphocreatine/adenosine triphosphate ratio as the potential mechanism by which weight loss improves diastolic function.⁴³⁾

In our study, 8% or more weight loss over a period of 1 year improved diastolic function and in parallel physical fitness resulting in a net gain of 65 m during 6-minute walking. As the 6-minute walk distance was lower at baseline in obese patients with LVDD compared to the obese without LVDD, it is implied the improvement of physical performance was related to the improvement of diastolic function. Although this may be evidence that changes in echocardiographic parameters translate to functional changes, other unspecified factors such as a decrease in oxygen demand by weight reduction, improved skeletal muscle function, etc. may also have an effect on the improvement of 6-minute walk distance after successful weight reduction in obese patients as well.

There are several limitations to our study. Although all data was gathered prospectively, the separation of patients according to successful weight reduction was retrospective. In the present study successful weight loss was classified as at least 8% of baseline weight at the end of the 1-year program. We specified this according to the average weight reduction achieved using different modes of weight loss strategies at our department. However, similar results were obtained using different cutoffs, ie, 10% of baseline weight (data not shown). In this regard, it would be also helpful to analyze the alteration of diastolic function according to the time course of weight change (in example, rapid versus slow) and weight stability (or lack thereof) in the later months, both of which can affect the outcomes. However, in our study the numbers of cases for such a subgroup analysis are currently too small for meaningful statistical analysis. Another limitation is that Doppler echo was used to determine LVDD and not invasive testing or symptomatic assessment. Criteria used to determine LVDD in the study were in part heart rate, preload and afterload dependent and are subject to change within any given patient. Furthermore, when studying obese subjects, echocardiographic measurements may be error-prone or imprecise. However, reliability analysis performed with interobserver agreement statistics shows that concordance correlation at least for Doppler measurements was high.

In conclusion, diastolic dysfunction seen in severe obesity may be in part reversible by successful weight reduction.

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Supplemental Table I, II
Supplemental Figure 1, 2, 3
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