Effects of Intensive Lifestyle Intervention and Gastric Bypass on Aortic Stiffness: A 1-Year Nonrandomized Clinical Study

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Objective: To compare the long-term effects of Roux-en-Y gastric bypass (GBS) and intensive lifestyle intervention (ILI) on aortic stiffness.

Methods: Nonrandomized clinical trial. Aortic stiffness was assessed by carotid-femoral pulse wave velocity ($c_P W V$) using high-fidelity applanation tonometry.

Results: A total of 159 treatment-seeking morbidly obese patients were included, 82 (54 females) in the GBS-group and 77 (48 females) in the ILI-group. Participants in the GBS-group were younger (42.0 ± 9.9 vs. 46.4 ± 10.5 years), heavier (BMI 45.7 ± 5.3 vs. 42.0 ± 4.9 kg/m2), and had lower systolic pressure (137 ± 19 vs. 145 ± 18 mm Hg) and pulse pressure (57 ± 16 vs. 65 ± 17 mm Hg), all $P$ ≤ 0.006. Mean (SD) $c_P W V$ at baseline was 8.6 ± 1.7 m/s in the GBS-group and 8.6 ± 1.9 m/s in the ILI-group, $P$ = 0.959. At follow-up, mean (95% CI) weight loss was larger in the GBS-group than in the ILI-group −43.3 (−46.0 to −40.7) vs. −12.1 (−14.6 to −9.6) kg, $P$ < 0.001. The mean change in $c_P W V$ was −0.02 (−0.31 to 0.27) m/s in the GBS-group and 0.03 (−0.28 to 0.33) m/s in the ILI-group, both $P$ ≥ 0.412; adjusted between-group difference (ANCOVA) 0.05 (−0.40 to 0.49) m/s, $P$ = 0.836. The adjusted regression analysis showed that weight loss was associated with increased $c_P W V$ in the GBS-group.

Conclusions: GBS and ILI had no significant long-term effects on aortic stiffness in treatment-seeking morbidly obese individuals.

Introduction

Obesity is a global health concern of epidemic proportions (1) and is associated with increased risk of diabetes, obstructive sleep apnea, cardiovascular disease (CVD), some cancer types and premature death (2). The cornerstone of obesity management is weight loss, and both dietary and surgically induced weight loss improve the CVD risk profile in terms of reduced blood pressure, blood glucose, and lipid levels in morbidly obese individuals (3). In addition, increased aerobic fitness and physical activity improve CVD risk independent of weight loss, especially in unfit overweight and obese individuals (4). CVD risk assessment in obese individuals is largely based on established risk estimates such as the Framingham Risk Score which emphasizes smoking habits, lipid levels, and blood pressure (5).

Aortic stiffness provides additional information regarding CVD risk beyond traditional risk factors (6). Further, unlike fluctuating risk factors like blood lipids, glucose, and hypertension, aortic stiffness represents the accumulated damaging effects of all these measures over time (7). Aortic stiffness is largely determined by structural changes in the arterial wall such as (1) increased collagen-elastin ratio, (2) fractures of elastic lamella and the cross-linking of collagen, and (3) increased amount of advanced glycation end-products. Structural changes in aorta occur slowly over a period of years (8) while other factors like adrenergic activity and aerobic exercise may modulate aortic compliance over a short space of time (9,10). Aortic stiffness is considered a valid surrogate end point of CVD (7) and is also an independent predictor of all-cause mortality (7) and cardiovascular morbidity and mortality (7,11,12). Carotid to femoral pulse wave velocity ($c_P W V$) has been recommended as the gold-standard measure of aortic stiffness (13,14).

Some short-term (<12 months) studies have shown reduced aortic stiffness after various lifestyle intervention programs in normal weight (15), overweight (16), obese (17), and morbidly obese patients (18). Similarly, some long-term (≥1-year) studies have demonstrated beneficial effects of weight loss on aortic stiffness in metabolically healthy obese patients after diet alone (19), diet and physical activity (20), and diet or bariatric surgery (21). In addition, one study demonstrated reduced $c_P W V$ after weight loss in obese diabetic patients (22). However, the comparative effect of bariatric

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EG and NN conducted all measurements. EG, JH, and NN analyzed data. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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surgery and intensive lifestyle intervention (ILI) on aortic stiffness remains unknown.

The primary aim of this study was to compare the 1-year effect of an ILI program and a surgical weight loss program on cfPWV in morbidly obese individuals. Our main hypothesis was that patients who underwent Roux-en-Y gastric bypass surgery (GBS) after an initial low calorie diet would have a larger mean 1-year reduction of cfPWV compared to those who underwent an ILI program.

Methods
Study design
This is the second part of a nonrandomized clinical trial comparing the effects of an ILI and an initial 7-week low-calorie diet (LCD) followed by GBS on aortic stiffness in treatment-seeking morbidly obese patients (Clinical Trials.gov Identifier NCT00626964). Preliminary results from baseline (23), and short-term results after 7 weeks (18) are published elsewhere. The protocol was approved by the regional ethics committee of the Southern Norway Regional Health Authority (identifier S-05175). All procedures were conducted according to the principles expressed in the Declaration of Helsinki (24). Written informed consent was provided by all participants.

Setting
The present study was conducted at the Morbid Obesity Center, Vestfold Hospital Trust, from February 2008 to June 2012. Before inclusion, patients were either assigned to an ILI program at the Clinic of Physical Medicine and Rehabilitation (CPMR) or to an initial LCD followed by GBS at the Morbid Obesity Center (MOC).

Participants
All participants were recruited from our tertiary care center. For practical reasons and to maximize compliance, participants had to reside within 100 km of either the CPMR or MOC. The patients in the ILI-group were all selected from patients that had registered for participation in a standardized health promotion and weight reduction program at the CPMR. Participants in the GBS-group were selected from patients as a result of undergoing bariatric surgery at our hospital. The decision regarding the type of intervention to be undertaken was made prior to inclusion to the present study and was not part of the protocol.

Inclusion criteria were BMI ≥ 35 kg/m² with at least one obesity-related comorbidity, or a BMI ≥ 40 kg/m². Patients were excluded if they had uncompensated heart failure, cardiac arrhythmias, unstable angina, end-stage renal disease, bleeding disturbances, serious psychiatric disorders, serious eating disorders, cardiac pacemakers, intra-cardiac devices, or a recent cerebrovascular event or myocardial infarction (within the past 6 months).

Interventions
The first 7 weeks of ILI is described in detail elsewhere (18). Briefly, the ILI included both a dietary and physical intervention. The first year of the intervention was divided into two stages (Figure 1). The first 12 weeks included treatment sessions 3 days per week, with patients participating in two supervised training sessions for 60-90 min and lectures on nutrition, physical activity, and motivation each day. Patients received a dietary plan with an energy restriction of 1000 kcal/day of the calculated total energy expenditure at baseline (25). Study participants had individual sessions with qualified personnel who used elements of a lifestyle modification intervention in order to invoke behavioral change in the participants. During weeks 13-52, patients received monthly follow-up, alternating between group-based and individual sessions every other month. Patients were advised to maintain physical activity for 60-90 min per day in order to increase or maintain weight loss (26), and during the individual sessions patients were told to describe their physical activity level.

Preceding surgery, patients in the GBS-group completed a 7-week LCD (< 900 kcal per day; Figure 1). Laparoscopic Roux-en-Y GBS were performed in 94 patients. The gastric pouch was about 25 ml.
while the intestinal limb lengths were measured as follows: alimentary limb 120 cm, biliopancreatic limb 60 cm, and common channel, variable length. A standardized regimen of dietary supplements and a proton pump inhibitor were prescribed to all patients after surgery.

Outcomes
The main outcome variable was the 1-year change in aortic stiffness measured by cPWV. Secondary outcome variables were changes in blood pressure, body weight, and body composition.

Data source and measurements
Detailed descriptions of data sources and measurements are published elsewhere (18). Briefly, all participants underwent medical examinations which included collection of blood samples, measurement of body weight, height, and waist circumference, and analysis of body composition using bioelectrical impedance analysis (Inbody 720, Body Composition Analyzer, Biospace, Seol, South Korea). Resting blood pressure was measured using an electronic blood pressure recorder with an appropriately sized cuff (Dinamap®, ProCare Series, G.E. Medical Systems, Buckinghamshire, UK) with the patient sitting in an upright position. Arterial hypertension was defined by either a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or the use of antihypertensive medication. Ischemic heart disease was defined as a history of stable coronary artery disease, percutaneous coronary intervention, coronary artery bypass graft surgery, or myocardial infarction. Mean arterial pressure (MAP) was calculated as [diastolic pressure x 2] + systolic pressure]/3 (27). Type 2 diabetes was diagnosed in patients who had a prior history of type 2 diabetes or a fasting serum glucose level ≥7.0 mmol/L (28). Model Assessment Insulin Resistance (HOMA-IR) was calculated as [fasting serum glucose (mmol/L) x fasting serum insulin (pmol/L)]/135 (29) and low-density lipoprotein cholesterol (LDL) concentrations were estimated using the Friedewald equation (30).

The SphygmoCor® system (AtCor Medical, Sydney, Australia) and a single high-fidelity applanation tonometer (Millar®) were used to measure cPWV. Pulse waves were obtained sequentially from the carotid and femoral artery. The travel distance was calculated by subtracting the distance between the carotid artery and the sternal notch from the distance between the sternal notch and the femoral artery (13). The subtracted travel distance measured at baseline was used in the calculations of cPWV at follow-up.

Physical activity level was measured with a self-reported questionnaire (CONOR) (31) at 59 weeks follow-up. The questionnaire divides physical activity into two main parts: leisure time physical activity and occupational physical activity. Physical activity during leisure time was further divided into light physical activity (not sweaty and breathless) and vigorous physical activity (sweaty and breathless), and scored according to duration (hour/week) (none, <1, 1-2, >3). Occupational physical activity was scored according to type of work (mainly sedentary, mainly walking, mainly walking or/and carrying, heavy manual labor).

Laboratory analyses
Analyses of serum glucose and blood lipids were performed using dry reagent slide technology on the Vitros FS 5.1 (Ortho-Clinical Diagnostics, NY, USA). Glycated hemoglobin (HbA1c) was analyzed using high performance liquid chromatography on Tosoh HLC-723 G7 (Tosoh Corporation, Tokyo, Japan). Sera for analysis of insulin were stored at −20°C and analyzed within 1 week of blood sampling (Linco Research, St. Charles, MO).

Sample size
The sample size was calculated based on a publication demonstrating a mean reduction of 1.4 m/s in cPWV after 8% nonsurgical weight loss (22). We anticipated a mean 1 year weight loss of 8% and 30%, and a mean ± SD reduction in cPWV of 1.4 ± 2.8 and 2.8 ± 6.2 m/s, in the lifestyle and surgery groups, respectively. To show a statistically significant difference between the two groups at a power of 80% (α = 0.05), at least 126 individuals (63 in each group) had to complete the study. To allow for a drop-out rate of < 40% it was necessary to include 200 patients (100 in each group).

Statistical methods
Data are presented as mean ± SD or number (%) unless otherwise specified. Differences between groups at baseline were analyzed using independent samples t-tests for continuous variables and Fisher’s exact tests for categorical variables. Within-group changes from baseline to follow-up were analyzed using paired samples t-tests for continuous data and McNemar’s test for categorical data. The
potential interaction between gender and treatment choice was analyzed using two-way analysis of covariance. The difference in cfPWV between groups at 59 weeks follow-up were analyzed using one-way analysis of covariance (ANCOVA) including age, gender, history of coronary artery disease, baseline BMI, MAP, heart rate, and cfPWV as covariates. Differences in systolic blood pressure, diastolic blood pressure, and pulse pressure at follow-up were analyzed using ANCOVA including age, gender, baseline BMI, history of coronary artery disease, baseline BMI, MAP, heart rate, and cfPWV as covariates.

| TABLE 1 Baseline characteristics, body composition, and cardiovascular risk factors among 159 morbidly obese patients who completed the study according to treatment choice |
|-------------------------------------------------|---------------------------------|---------------------------------|
| Age (years)                                     | 46.4 ± 10.5                     | 42.0 ± 9.9                      | 0.006                           |
| Gender, female (%)                              | 48 (62)                         | 54 (66)                         | 0.741                           |
| Diabetes (%)                                    | 17 (22)                         | 24 (29)                         | 0.365                           |
| Hypertension (%)                                | 59 (78)                         | 50 (61)                         | 0.026                           |
| Ischemic heart disease (%)                      | 12 (16)                         | 2 (2)                           | 0.004                           |
| Smokers (%)                                     | 8 (10)                          | 17 (21)                         | 0.084                           |
| Weight and anthropometric measures              |                                 |                                 |                                 |
| Weight (kg)                                     | 124 ± 20                        | 137 ± 22                        | <0.001                          |
| Body mass index (kg/m²)                         | 42.0 ± 4.9                      | 45.7 ± 5.3                      | <0.001                          |
| Waist circumference (cm)                        | 126 ± 12                        | 132 ± 12                        | 0.001                           |
| Fat mass (kg)                                   | 57.6 ± 12.1                     | 66.5 ± 12.5                     | <0.001                          |
| Skeletal muscle mass (kg)                       | 37.5 ± 7.2                      | 39.4 ± 8.1                      | 0.120                           |
| cfPWV and blood pressure                        |                                 |                                 |                                 |
| Pulse wave velocity (carotid femoral) (m/s)     | 8.6 ± 1.9                       | 8.6 ± 1.7                       | 0.959                           |
| Systolic blood pressure (mm Hg)                 | 145 ± 18                        | 137 ± 19                        | 0.006                           |
| Diastolic blood pressure (mm Hg)                | 81 ± 11                         | 79 ± 13                         | 0.523                           |
| Pulse pressure (mm Hg)                          | 65 ± 17                         | 57 ± 16                         | 0.002                           |
| Mean arterial pressure (mm Hg)                  | 102 ± 11                        | 99 ± 14                         | 0.074                           |
| Heart rate (beats/min)                          | 79 ± 13                         | 77 ± 14                         | 0.288                           |
| Glucose and lipid metabolism                    |                                 |                                 |                                 |
| Insulin (pmol/L) †                              | 87 (48, 115)                    | 93 (58, 140)                    | 0.144                           |
| Glucose (mmol/L) †                              | 5.3 (4.9, 6.4)                  | 5.4 (5.1, 6.4)                  | 0.248                           |
| HbA1c (%) †                                     | 5.7 (5.4, 6.1)                  | 5.8 (5.3, 6.3)                  | 0.772                           |
| HOMA-IR †                                       | 3.4 (1.9, 5.7)                  | 4.1 (2.3, 6.2)                  | 0.157                           |
| Total cholesterol (mmol/L)                      | 5.1 ± 1.0                       | 4.9 ± 1.0                       | 0.287                           |
| LDL-cholesterol (mmol/L)                        | 3.1 ± 1.0                       | 3.1 ± 0.9                       | 0.936                           |
| HDL-cholesterol (mmol/L)                        | 1.2 (1.0, 1.4)                  | 1.1 (0.9, 1.3)                  | 0.072                           |
| Triglycerides (mmol/L) †                        | 1.4 (1.1, 2.1)                  | 1.5 (1.0, 2.0)                  | 0.820                           |
| Drugs                                           |                                 |                                 |                                 |
| Statins (%)                                     | 18 (23)                         | 12 (15)                         | 0.223                           |
| Any antihypertensive drugs (%)                  | 35 (46)                         | 29 (35)                         | 0.201                           |
| Beta blocker (%)                                | 14 (18)                         | 10 (12)                         | 0.376                           |
| Calcium channel blocker (%)                     | 12 (16)                         | 12 (12)                         | 0.647                           |
| Renin-angiotensin-aldosterone-system inhibitor (%) | 28 (36)                        | 23 (28)                         | 0.309                           |
| Diuretics (%)                                   | 18 (23)                         | 15 (18)                         | 0.442                           |
| Other blood pressure medications (%)            | 6 (8)                           | 4 (5)                           | 0.525                           |
| Any antidiabetic/glucose-lowering drugs (%)     | 18 (23)                         | 19 (23)                         | 0.999                           |
| Glitazone (%)                                   | 2 (3)                           | 5 (6)                           | 0.444                           |
| Sulfonylurea (%)                                | 5 (7)                           | 8 (10)                          | 0.567                           |
| Insulin (%)                                     | 4 (5)                           | 1 (1)                           | 0.999                           |
| Dipeptidyl peptidase-4 inhibitor (%)            | 0                               | 1 (1)                           | 0.999                           |
| Metformin (%)                                   | 12 (16)                         | 16 (20)                         | 0.540                           |

Values reported are number (%) or mean ± SD unless otherwise noted. Independent sample t-test was used for normally distributed data and Mann-Whitney for nonparametric data. Fischer’s exact test was used for categorical data. †Reported as Median (Q1, Q3) as a result of skewed distribution.
coronary artery disease, and baseline status in dependent variable as covariates.

In addition, we performed post hoc subgroup correlation analyses between changes in anthropometric variables and changes in cfPWV in the two treatment groups. Finally, multiple linear regression analyses with cfPWV-changes as effect variable and age, gender, history of coronary artery disease, and baseline values of BMI, mean arterial pressure, heart rate, cfPWV, and anthropometric parameters as explanatory variables were performed in each treatment group.

P-values below 0.05 were considered statistically significant. Particular attention should, however, be directed towards smaller P-values, i.e., those below 0.01, because a considerable number of P-values have been calculated.

Results
A total of 239 individuals were eligible, 39 declined to participate, leaving 200 (64% female) participants to be included in the study (Figure 2). During the first 7 weeks, 13 individuals in the ILI-group and seven individuals in the GBS-group withdrew. During the last period of 52 weeks an additional 13 patients in the ILI-group and nine patients in the GBS-group withdrew, while one patient re-entered the ILI-group at 59 weeks follow-up. This leaves 159 (64% female) completers (80% of all included patients) in the present analysis, a total number of 77 (76%) in the ILI-group and 82 (84%) in the GBS-group.

The GBS-patients were approximately 4 years younger, 13 kg heavier, and had lower systolic blood pressure, pulse pressure, and a lower prevalence of hypertension and ischemic heart disease compared to the ILI-patients. The treatment groups did not differ significantly in terms of cfPWV or in the use of antihypertensive drugs, lipid-lowering drugs, and antidiabetic drugs (Table 1).

Changes in aortic stiffness, blood pressure, and heart rate
The average cfPWV for completers in both groups at baseline, 7, and 59 weeks are shown in Figure 3. As previously reported (18), in the short term (7 weeks), the ILI-group had a significantly larger mean (95% CI) reduction of cfPWV than the GBS-group (low calorie diet; $-0.6 (-0.8, -0.4)$ m/s vs. $-0.2 (-0.4, 0.0)$ m/s, adjusted between-group difference 0.4 (0.1, 0.6) m/s, $P = 0.004$. In contrast, there were no significant changes in cfPWV from baseline to 59 weeks in either treatment group, and no significant adjusted between-group difference was found (Figure 3 and Table 2). No significant interaction between gender and treatment group was found ($P = 0.158$). Patients in the GBS-group had a significantly larger decline in heart rate compared to patients in the ILI-group and tended to have larger reductions of systolic and diastolic blood pressure (Table 2).

Impact of weight loss according to treatment group
Figure 4 illustrates that weight loss and reduced WC were associated with decreasing cfPWV in the ILI-group, but, in contrast, with increasing cfPWV in the GBS-group. After adjustments for age, gender, history of coronary artery disease, and baseline values of BMI, MAP, heart rate, and cfPWV, multiple linear regression analyses showed that the associations between changes in cfPWV and changes in WC, BMI, and body weight remained statistically significant in the GBS-group only (all $P < 0.006$).

Weight loss, glucose metabolism, and lipids
Patients in the GBS-group had, compared to patients in the ILI-group, a larger percentage weight loss, 32% vs. 10%, and greater reductions of mean waist circumference, fat mass, and skeletal muscle mass (Table 2).

Patients in the GBS-group also achieved larger reductions of serum insulin, glucose, HbA1c, HOMA-IR, total cholesterol, LDL cholesterol, and triglycerides, and a larger increase in mean HDL cholesterol compared to patients in the ILI-group (Table 2).

Changes in medications
The proportion of patients treated with any antihypertensive and antidiabetic drugs decreased significantly during the first 59 weeks in the surgery group only. Specifically, the number of GBS-patients treated with RAAS-inhibitors, beta blockers, and diuretics decreased from 23 to 13 (44%), 10 to 4 (60%), and 15 to 7 (53%), respectively, all $P < 0.032$. The number of patients using sulfonylurea or metformin decreased from 8 to 0 (100%) and 16 to 3 (81%), $P = 0.008$ and $P < 0.001$, respectively. There was no significant change in the use of statins in either group, both $P > 0.374$.

Physical activity level at follow-up
The majority of patients reported that they completed >3 hours/week of light physical activity and >3 hours/week of vigorous physical activity at follow-up, with no significant differences between groups (Supporting Information Table 1).

Discussion
Our results did not confirm the hypothesis that patients undergoing bariatric surgery would achieve a larger mean 1-year reduction of
TABLE 2 Within-group changes and adjusted between-group differences in carotid to femoral pulse wave velocity, blood pressure, heart rate, anthropometric measures, glucose metabolism, and lipids in 159 morbidly obese patients during the study

|                          | Intensive lifestyle intervention (n = 77) | Gastric bypass surgery (n = 82) | Adjusted difference between groups | P-value |
|--------------------------|-----------------------------------------|------------------------------|-----------------------------------|---------|
| Pulse wave velocity (carotid to femoral) (m/s) | 0.03 (–0.28 to 0.33) | –0.02 (–0.31 to 0.27) | 0.05 (–0.40 to 0.49) | 0.836 |
| Systolic blood pressure (mm Hg) | –2 (–6 to 3) | –8 (–13 to –4)* | 6 (0 to 13) | 0.057 |
| Diastolic blood pressure (mm Hg) | –1 (–3 to 2) | –4 (–6 to –2) | 3 (0 to 7) | 0.067 |
| Pulse pressure (mm Hg) | 0 (–4 to 4) | –5 (–9 to –2)** | 5 (0 to 10) | 0.074 |
| Mean arterial pressure (mm Hg) | –1 (–4 to 2) | –6 (–8 to –3)* | 4 (0 to 8) | 0.038 |
| Heart rate (beats/min) | –6 (–8 to –3)** | –11 (–14 to –9)** | 7 (3 to 10) | <0.001 |
| Weight (kg) | –12.1 (–14.6 to –9.6)** | –43.3 (–46.0 to –40.7)** | 27.6 (24.0 to 31.1) | <0.001 |
| BMI (kg/m²) | –4.0 (–4.9 to –3.2)** | –14.4 (–15.3 to –13.6)** | 9.3 (8.2 to 10.5) | <0.001 |
| Waist circumference (cm) | –10.9 (–13.2 to –8.6)** | –30.5 (–32.9 to –28.0)** | 17.1 (13.6 to 20.5) | <0.001 |
| Fat mass (kg) | –10.2 (–12.5 to –7.9)** | –36.6 (–38.9 to –34.3)** | 24.2 (20.9 to 27.5) | <0.001 |
| Skeletal muscle mass (kg) | –0.5 (–1.5 to 0.6) | –4.1 (–5.2 to –3.1)** | 3.3 (1.7 to 4.9) | <0.001 |
| Insulin (pmol/L) | –21 (–34 to –8)* | –81 (–102 to –59)** | 41 (28 to 55) | <0.001 |
| Glucose (mmol/L) | –0.4 (–0.8 to 0.1) | –1.2 (–1.6 to –0.8)** | 0.7 (0.3 to 1.1) | 0.002 |
| HbA1C (%) | –0.4 (–0.6 to –0.2)** | –0.8 (–1.0 to –0.5)** | 0.3 (0.1 to 0.4) | 0.001 |
| HOMA-IR | –1.0 (–1.7 to –0.3)* | –4.4 (–5.8 to –3.0)** | 2.0 (1.2 to 2.7) | <0.001 |
| Total cholesterol (mmol/L) | –0.1 (–0.2 to 0.1) | –0.6 (–0.8 to –0.4)** | 0.6 (0.3 to 0.8) | <0.001 |
| LDL cholesterol (mmol/L) | 0.0 (–0.2 to 0.2) | –0.7 (–0.8 to –0.5)** | 0.7 (0.5 to 0.9) | <0.001 |
| HDL cholesterol (mmol/L) | 0.1 (0.1 to 0.2)** | 0.3 (0.3 to 0.4)** | 0.2 (0.1 to 0.3) | <0.001 |
| Triglycerides (mmol/L) | –0.3 (–0.5 to –0.2)** | –0.7 (–0.8 to –0.5)** | 0.3 (0.2 to 0.5) | <0.001 |

1P < 0.05; 2P < 0.001

Adjusted within-group values. Mean (95% CI). Within-group changes of the various outcome variables (left column) were analyzed with paired-samples t-test. Analyses of covariance (ANCOVA) including age, gender, history of coronary artery disease, baseline BMI, MAP, heart rate, and baseline status in dependent variable as covariates for PWV, age, gender, history of coronary artery disease, baseline BMI, and baseline status in dependent variable as covariates for systolic blood pressure, diastolic blood pressure, and pulse pressure. Age, gender, and baseline status in dependent variable was included as covariates in ANCOVA analysis of heart rate, anthropometric measures, glucose metabolism, and lipids.

Obesity than controls completing an ILI-program. In addition, and to our surprise, despite considerable 1-year weight losses in both treatment groups (10% and 32%), the average PWV did not change significantly within either group. To our knowledge, this is the first study to compare the effect of bariatric surgery and an ILI-program on PWV. Previous studies, including our own, have demonstrated the beneficial short-term (7 weeks-6 months) effects of various lifestyle intervention programs on PWV in normal weight (15), overweight (16), and obese populations (17,18). In contrast, our results did not confirm the findings of some previous prospective long-term (1 year) studies demonstrating significant reductions of aortic stiffness after weight loss induced by diet alone (19), diet and physical activity (20), diet or bariatric surgery (21), and diet with/without orlistat (22). Rather, and to the contrary, the adjusted PWV remained stable in both the GBS- and the ILI-group 1 year after start of treatment.

The apparent discrepancy between previous studies and the present one might have several explanations. First, in contrast with our study of treatment-seeking morbidly obese subjects, several previous studies (19-21) included obese but otherwise healthy populations. It is plausible that subjects with obesity related comorbidities, like the majority of our patients, have a higher frequency of structural changes associated with aortic stiffness in the aortic wall than their metabolically healthy obese counterparts (9,10) and that the potential reversal of such changes may take several years (8). Further, one previous study included non-treatment-seeking diabetic, but otherwise healthy obese individuals (22). Approximately two-thirds of the participants achieved a decrease in PWV after 1 year, and individuals with the highest baseline values showed the largest improvement. This finding might partly be explained by regression to the mean, and the lack of adjustments for possible confounding factors could partly explain the difference in results compared to our own. Additionally, a significant number of participants in the GBS-group stopped taking antihypertensive and anti-diabetic drugs during the study. The former might partly explain the modest decrease in blood pressure and, as cfPWV is partly pressure dependent, the absence of beneficial changes in aortic stiffness in the surgical group. Infact, antihypertensive drugs may have a beneficial effect on cfPWV. In addition, the use of metformin (33) and statins (34) have been associated with reduced arterial stiffness. The discontinuation of metformin might also have worked against any weight loss induced decline in PWV.

Importantly, aortic stiffness is influenced by both functional and structural factors (9,10,35,36). The results from the present analysis demonstrate that the short-term reduction of PWV observed after 7 weeks of ILI (18) was a temporary one, and thus likely to be mediated by changes in functional factors like increased physical fitness,
decreased heart rate and blood pressure and decreased activity in the sympathetic nervous system (9,10). The findings that the greatest reductions in heart rate and blood pressure as well as cfPWV throughout the study period were observed in the ILI-group after 7 weeks of follow-up also support this. Accordingly, the small long-term reductions in blood pressure and heart rate might partly explain the lack of association between treatment choice and changes in cfPWV as shown in the present study.

Post hoc subgroup analyses did not reveal any significant association between weight loss and changes in cfPWV after lifestyle intervention, which is in accordance with the negative findings from the SAVE trial (37). The apparent detrimental effect of surgically induced weight loss on arterial stiffness was somewhat surprising and difficult to explain. Importantly, given the well known limitations of post hoc subgroup analyses, this finding should be interpreted with caution (38). One might, however, speculate that a massive weight loss may lead to a reflex increase in arterial resistance as the hypo-responsive baroreflex caused by obesity related chronic vasodilatation is abolished (39).

It is unlikely that our results are biased by measurement error since all measurements were conducted at one center by two trained operators (EG and NN), both of whom were present at all measurements.
Our findings are further strengthened by the relatively large sample size, long follow-up time and a considerable weight loss following both interventions. In addition, all of the physical exercise sessions in ILI were supervised by qualified personnel.

The major limitation of the study is the nonrandomized design. Since both treatments are publicly funded and patients are supposed to take an active role in a decision over treatment choice (40), we found it ethically most appropriate to perform a nonrandomized comparative study. Other minor limitations include the lack of data describing patients’ adherence to the prescribed interventions (diet and physical activity) and the use of self-reported use of medications and level of physical activity. In addition, the use of sequential measurements at the carotid and femoral sites might have affected the reliability of the $cPWV$ measurements. However, to minimize this potential bias $cPWV$ was measured three times at each measurement point, and the averages of these measurements were used in the calculations. Finally, we cannot exclude the possibility of a false negative result (type 2-error), but a post-hoc power analysis based on the number of participants completing the study demonstrated a power of more than 80% to detect a clinically meaningful between-group difference in $cPWV$ change of 0.6 m/s ($\alpha = 0.05$).

**Perspective**

Aortic stiffness measured by $cPWV$ is not only a measure of age-related aortic stiffening (10), but also a potential risk factor for cardiovascular disease (7). The findings of the present study suggest that long-term aortic stiffness in morbidly obese individuals is not significantly influenced by weight loss following bariatric surgery or an intensive lifestyle program. Our findings need further verification in future studies.

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