Sympathetic crosstalk in the cardiorenal axis

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Blood pressure reduction after gastric bypass surgery is explained by a decrease in cardiac output

胃バイパス手術後の血圧低下について説明します 心拍出量の減少による。

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ABSTRACT

Background

Blood pressure (BP) decreases in the first weeks after Roux-and-Y gastric bypass surgery. Yet, the pathophysiology of the BP lowering effects observed after gastric bypass surgery are incompletely understood.

Methods

We evaluated BP, systemic hemodynamics and baroreflex sensitivity in 15 obese women (mean age 42±7 yrs., body mass index 45±6 kg/m^2) two weeks before and six weeks following Roux-and-Y gastric bypass surgery.

Results

Six weeks after gastric bypass surgery mean body weight decreased by 13±5 kg (10%, p<0.001). Office blood pressure (BP) decreased from 137±10/86±6 to 128±12/81±9 mmHg (p<0.001, p<0.01), while daytime ambulatory BP decreased from 128±14/80±9 to 114±10/73±6 mmHg (p=0.01, p=0.05), whereas night-time BP decreased from 111±13/66±7 to 102±9/62±7 mmHg (p=0.04, p<0.01). The decrease in BP was associated with a 1.6±1.2 L/min (20%, *p*<0.01) decrease in cardiac output (CO), while systemic vascular resistance increased (153±189 dyn·s·cm^{-5}, 15%, *p*<0.01). The maximal ascending slope in systolic blood pressure decreased (192 mmHg/s, 19%, p=0.01), suggesting a reduction in left ventricular contractility. Baroreflex sensitivity increased from 9.0 [6.4-14.3] to 13.8 [8.5-19.0] ms·mmHg^{-1} (median [IQR]; *p*<0.01) and was inversely correlated with the reductions in heart rate (R= -0.64, *p*=0.02) and CO (R= -0.61, *p*=0.03). In contrast, changes in body weight were not correlated with changes in either BP or CO.

Conclusions

The BP reduction following Roux-and-Y gastric bypass surgery is correlated with a decrease in CO independent of changes in body weight. The contribution of heart rate to the reduction in CO together with enhanced baroreflex sensitivity suggests a shift towards increased parasympathetic cardiovascular control.

NEW AND NOTEWORTHY

The reason for the decrease in blood pressure (BP) in the first weeks after gastric bypass surgery remains to be elucidated. We show that the reduction in BP following surgery is caused by a decrease in cardiac output (CO). In addition, the maximal ascending slope in systolic blood pressure decreased suggesting a reduction in left ventricular contractility and cardiac workload. These findings help to understand the physiological changes following surgery and are relevant in light of the increased risk of heart failure in these patients.

Background

The prevalence of severe obesity is rapidly increasing.[1] Adiposity is related to BP and the development of hypertension[2,3], thereby contributing to the risk of cardiovascular disease. A pooled analysis of prospective studies has shown that every 5 kg/m² increase in body mass index (BMI) is associated with an approximate 30% increase in overall mortality and a 40% increase in cardiovascular mortality.[3,4] The increased risk of cardiovascular disease related to obesity mainly relates to an increased risk of ischemic heart disease and heart failure.[5,6] A recent population-based prospective study comprising more than 60,000 men and women showed that, in contrast to ischemic heart disease, the risk of heart failure was increased in both metabolically healthy and unhealthy obese subjects.[6]

Gastric bypass surgery has been shown to decrease the risk of mortality, particularly from diabetes and cardiovascular causes [7], part of which may be mediated by a decrease in BP.[8,9] The pathophysiology of the decrease in BP after gastric bypass surgery however is less well understood. The BP decrease is largest within the first few weeks and attenuates after the first few months following gastric bypass surgery.[9–11] Ahmed et al. previously reported that the largest drop in BP occurred after one week following gastric bypass surgery suggesting an important role for neurohormonal mechanisms.[10] Previous studies have shown that the BP increase is associated with changes in sympathovagal balance, both in obese normotensive and in lean hypertensive subjects.[12] Weight loss reduces muscle sympathetic nerve activity (MSNA), plasma norepinephrine concentration and increases baroreflex sensitivity

(BRS) as a reflection of less sympathetic and more parasympathetic dominance.[13–15] These changes in sympathovagal balance may differentially affect CO and systemic vascular resistance (SVR). Because morbid obesity confers a high CO state without a profound increase in SVR,[16] we hypothesized that the BP reduction after gastric bypass surgery would result from a more profound decrease in CO than in SVR and that these changes would be related to a change in sympathovagal balance.
Therefore, we assessed the short term effects of gastric bypass surgery on BP and systemic hemodynamics in morbidly obese normotensive and mildly hypertensive women. In addition, we examined the effect of gastric bypass surgery on baroreflex cardiovascular control.

METHODS

Study participants and design

Fifteen obese women participating in an observational study on the short-term effects of Roux and Y gastric bypass surgery were included. Participants were recruited from outpatient clinics of the Rijnstate Hospital, Arnhem and the Slotervaart Hospital, Amsterdam, the Netherlands, from October 2008 until December 2010. The patients were eligible for the study if they were scheduled for Roux and Y gastric bypass surgery, were older than 18 years and were able to give informed consent. Exclusion criteria were: 1) insulin dependent diabetes mellitus; 2) malignant or uncontrolled hypertension (BP>200/120 mmHg or BP>180/110 mmHg with 1 or more antihypertensive drugs, or >160/100 with 2 or more antihypertensive drugs); 3) a recent history (6 months or less) of substantial alcohol or drug abuse; 4) the use of antipsychotic medication or antidepressant medication; 5) somatic illness (except hypertension, hyperlipidaemia, diabetes mellitus treated with oral glucose lowering drugs), including neoplasm, active infection and abnormalities in the brain. We report weight loss in kg as percentage of total body weight. The study was carried out in accordance with the Declaration of Helsinki and approved by the Medical Ethical Committee of the AMC. All participants gave written informed consent.

Blood pressure

Hemodynamic measurements were performed two (±one) weeks before and six (±one) weeks after surgery in the morning after an overnight fast. After 10 minutes rest in supine position, BP was measured 3 times at 1-minute intervals on the left arm using a validated oscillometric device (Omron 705IT, Omron Healthcare Europe BV,

Hoofddorp, the Netherlands). We used the mean of the last two BP measurements as peripheral BP. Central BP measurements were performed using the SphygmoCor system (Atcor Medical Pty Ltd, West Ryde, Australia) as described previously.[17] Briefly, pressure waveforms were recorded from the radial artery of the left arm with applanation tonometry using a high-fidelity micromanometer (Millar Instruments, Texas, USA). Brachial systolic and diastolic BP were used for calibration of the radial waveform. With a generalized transfer function, the central aortic waveform was generated from which central systolic BP, pulse pressure (PP) and augmentation index (AIx) were calculated. AIx was corrected for heart rate of 75 beats per minute. Measurements were done in duplicate and means were used for analysis. Pulse pressure amplification (PPA) was defined as peripheral PP divided by central PP. Twenty-four-hour BP was assessed using an automatic ambulatory BP monitor (ABPM; Spacelabs 90207, Spacelabs Inc., Redmond, Washington, USA), which was placed on the non-dominant arm. The ABPM was programmed to record BP every 15 min during the day (07:00 – 23:00 h) and every 30 min at night (23:00 – 07:00 h). The ABPM assessment was accepted when at least 70% of measurements were available for analysis. We calculated 24-hour, day-time (07.00-23.00) and night-time (23.00-07.00) averages.

Systemic hemodynamics

Systemic hemodynamics were measured with the Nexfin device (BMEYE BV, Amsterdam, the Netherlands), which uses the volume-clamp method to non-invasively measure continuous finger arterial BP.[18,19] The finger cuff was applied to the third finger of the dominant arm, while brachial BP was reconstructed from the finger arterial pressure.[20] Mean arterial pressure (MAP) was calculated by taking the true integral of the arterial pressure wave over 1 beat divided by the corresponding beat interval. Stroke volume (SV) was determined by the pulse contour method (Nexfin CO-trek) as previously described.[21] Cardiac output (CO) was SV times heart rate (HR), cardiac index (CI) was CO corrected for body surface area and SVR the ratio of MAP and CO. Cardiac output (CO) was HR times SV. The maximal ascending slope of the pressure wave, calculated as the maximal value of the first derivative of the pressure pulse (dP/dt_{max}), was used to estimate changes in left ventricular contractility. Hemodynamic parameters were assessed after 15 minutes of supine rest and we used the average of a three-minute recording.

Baroreflex sensitivity

Baroreflex sensitivity (BRS) was obtained in the supine position from 5 min beat-to-beat SBP and inter-beat interval data. Estimates of BRS were obtained in the frequency-domain (BRS_{FD}) by Fourier Transform[22] and in the time-domain (BRS_{TD}) by the sequence method.[23,24] For BRS_{FD}, beat-to-beat SBP and inter beat interval (IBI) time series were detrended using a Hanning window. Power spectral density and cross-spectra of systolic BP variability (BPV) and heart rate variability (HRV) were computed using discrete Fourier transform. The low (LF; 0.06 – 0.15 Hz) and high frequency band (HF; 0.15 – 0.4 Hz) were selected and BPV_{LF}-to-HRV_{LF} transfer gain was computed for coherence >0.5. Estimates of BRS_{TD} were obtained from beat-to-beat systolic BP and IBI data. The cross-correlation between 10 s series of systolic BP and IBI samples was computed for delays τ in IBI of 0-5 s. The τ yielding the highest cross-correlation was selected if significant with α set at 0.05. The regression slope was recorded as one BRS_{TD} value. Subsequently, the process was repeated for series of systolic BP and IBI samples 1 s later.

Statistical analysis

We assumed, based on previous studies examining the decrease in BP following bariatric surgery to find a 9 mmHg [10] drop in 24-hour systolic BP assuming a standard deviation (SD) of 8.3 mm Hg, [25] resulting a sample size of 9 patients using paired observations. To account for drop outs or measurements that failed to fulfil ambulatory BP measurement standards we included 15 patients.

Outcome data were tested for normality using Kolmogorov-Smirnov test. Values are expressed as mean ±standard deviation (SD) for normally distributed data and median [interquartile range] for non-normally distributed data. Paired Student's t-tests and Wilcoxon Signed Ranks Test were used where appropriate, to evaluate differences. Agreement between BRS_{TD} and BRS_{FD} was evaluated using intraclass correlation coefficient (ICC), based on a two-way mixed effects model with absolute agreement. Correlations are expressed as Pearson's correlation coefficient. Analyses were performed using SPSS, version 16.0 (Chicago, IL, USA).

RESULTS

Patient characteristics

Baseline characteristics of the 15 female participants are shown in table 1. At baseline, mean age was 42±7 years, mean BMI was 45±6 kg/m^2. The mean decrease in weight was 13±5 kg (10%) after six weeks (p<0.001).

Table 1. Baseline characteristics

n = 15	**Mean, SD**
Age*, yrs (SD)*	42 ±7
Height*, cm*	168 ±8
Weight*, kg*	126 ±20
BMI*, kg/m^2*	45 ±6
SBP*, mmHg*	137 ±10
DBP*, mmHg*	86 ±6
Fasting glucose*, mmol/L*	5.8 ±0.8
TC, *mmol/L*	4.4 ±0.6
LDL-C*, mmol/L*	2.7 ±0.5
HDL-C*, mmol/L*	1.1 ±0.2
Triglycerides*, mmol/L*	1.3 ±0.7
Use of antihypertensive medication	**n, (%)**
Beta blocker, *n (%)*	3 (20)
Thiazide diuretic, *n (%)*	3 (20)
ACEi/ARB, *n (%)*	2 (13)

Data are mean ±SD. BMI= body mass index, SBP= systolic blood pressure, DBP= diastolic blood pressure, TC= total cholesterol; LDL-C= low density lipoprotein cholesterol; HDL-C= high density lipoprotein cholesterol; ACEi= angiotensin converting enzyme inhibitor; ARB= angiotensin II receptor blocker.

Blood pressure

BP parameters before and after gastric bypass surgery are presented in table 2. All BP parameters showed a significant decrease six weeks after gastric bypass surgery. Peripheral systolic and diastolic BP decreased significantly from baseline by 9±5/5±6 mmHg (p<0.001/p<0.01), peripheral PP decreased 4±4 mmHg (p<0.01). Central SBP was 7±6 mmHg lower after surgery (p<0.001), while central PP tended to decrease (p=0.13). AIx and PPA did not change after gastric bypass surgery. Ambulatory 24-hour BP data with at least 70% successful readings were available for 10 patients. Twenty-four-hour ambulatory BP decreased by 11±11/5±6 mmHg (p<0.01/p=0.02). Day-time BP seemed to decrease more (14±14/7±8 mmHg, p=0.01/p=0.02) than night-time BP (8±11/4±5 mmHg, p=0.04/p=0.04).

Hemodynamics

Systemic hemodynamics before and after gastric bypass surgery are shown in table 3. Individual data of the hemodynamic measurements are shown in figure 1. After surgery MAP decreased by 7±7 mmHg (7%; p<0.01). HR decreased with 11±7 bpm (15%, p<0.001) and SV with 6±9 ml (5%, p=0.03) resulting in a 1.6±1.2 L/min (20%) lower CO (p<0.001). The CI decreased with 0.6±0.5 L/min/m² (17%, p=0.001). SVR increased by 153±189 dyn.s/cm^5 (15%, p<0.01) and dP/dt_{max} decreased by 192 mmHg/s (19%, p=0.01). Body weight was not related to changers in either CO (R=0.04, p=0.89) or dP/dt_{max} (R=-0.09, p=0.74).

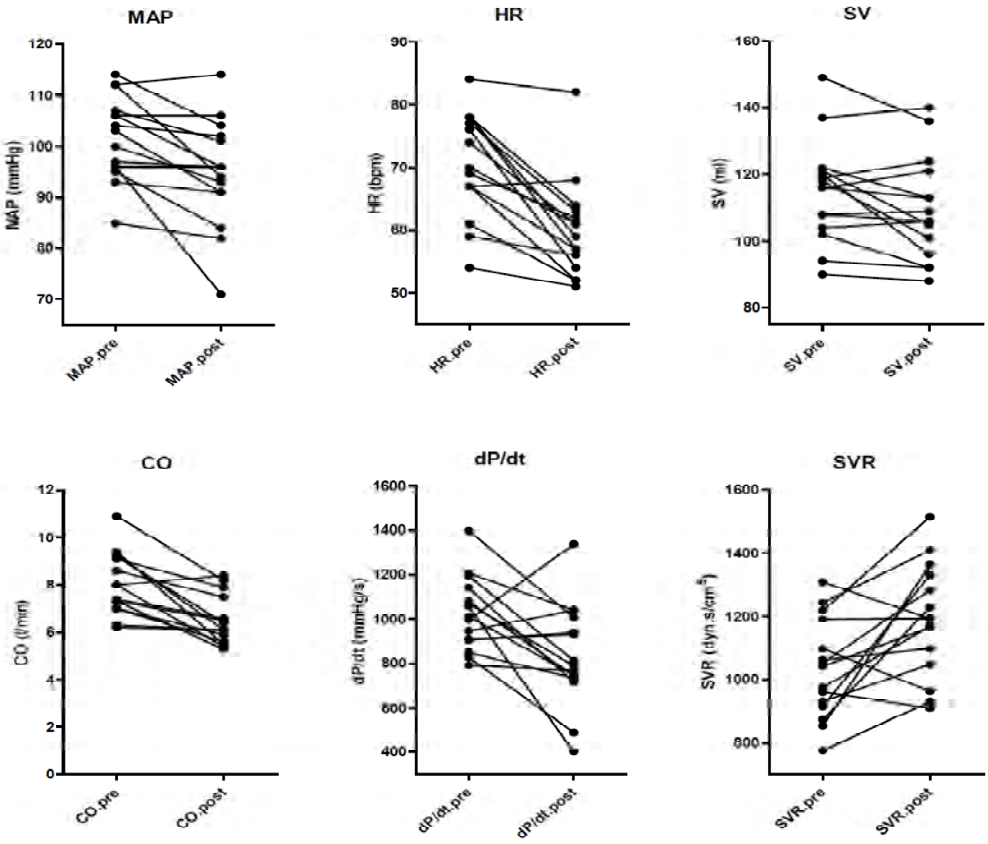

Figure 1. Hemodynamic Data. Individual data of mean arterial pressure (MAP), heart rate (HR), stroke volume (SV), cardiac output (CO), left ventricular contractility (dP/dt) and systemic vascular resistance (SVR) before and after bariatric surgery.

Table 2. Blood pressure before and after gastric bypass surgery.

Parameter	Before	After	p-value
Peripheral SBP, *mmHg*	137±10	128±12	<0.001
Peripheral DBP, *mmHg*	86±6	81±9	<0.01
Peripheral PP, *mmHg*	51±6	47±7	<0.01
Central SBP, *mmHg*	125±11	118±14	<0.001
Central PP, *mmHg*	38±6	36±8	0.13
PPA	1.36±0.1	1.32±0.2	0.14
AIx, %	19±11	16±13	0.08
24 hr SBP, *mmHg*	122±13	110±9	<0.01
24 hr DBP, *mmHg*	74±7	69±5	0.02
24 hr HR, *bpm*	84±8	71±8	<0.001
Day-time SBP, *mmHg*	128±14	114±10	0.01
Day-time DBP, *mmHg*	80±9	73±6	0.02
Day-time HR, *bpm*	88±8	77±9	<0.001
Night-time SBP, *mmHg*	111±14	103±9	0.04
Night-time DBP, *mmHg*	67±8	63±6	0.04
Night-time HR, *bpm*	77±9	62±8	<0.001

Data are mean ±SD. SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; PPA = pulse pressure amplification; AIx = augmentation index; HR = heart rate.

Baroreflex Sensitivity

BRS_{TD} and BRS_{FD} increased with sufficient agreement (ICC=0.92; p<0.001) following RYGBS (Table 4). BPV and HRV all tended to increase after surgery without reaching statistical significance.

Table 3. Systemic hemodynamics before and after gastric bypass surgery

Parameter	Before	After	*p-value*
MAP, *mm Hg*	102±8	95±11	<0.01
HR, bpm	71±8	60±8	<0.001
SV, *ml*	115±15	109±16	0.03
CO, *L/min*	8.1±1.3	6.5±1.0	<0.001
CI, *L/min*	3.5±0.5	3.0±0.5	0.001
SVR, $dyn{\cdot}s/cm^{5}$	1033±156	1186±177	<0.01
dP/dt, *mmHg/s*	1026±165	834±230	0.01

Systemic hemodynamic data were obtained using non-invasive finger arterial blood pressure monitoring. Data shown are means ±SD. MAP = mean arterial pressure; HR = heart rate; SV = stroke volume; CO = cardiac output; CI = cardiac index; SVR = systemic vascular resistance

Table 4. Baroreflex sensitivity and heart rate variability at baseline and after gastric bypass surgery.

Parameter	Before	After	*p-value*
BRS_{TD}, $ms{\cdot}mmHg^{-1}$	9.0 [6.4-14.3]	13.8 [8.5-19.0]	<0.01
BRS_{FD}, $ms{\cdot}mmHg^{-1}$	10.3 [7.3-14.3]	11.9 [8.3-22.8]	0.02
BPV_{LF}, $mmHg^{2}{\cdot}Hz^{-1}$	3.2 [2.0-5.9]	5.2 [1.5-9.3]	0.78
HRV_{LF}, $ms^{2}{\cdot}Hz^{-1}$	532 [272-1588]	1778 [297-2735]	0.50
HRV_{HF}, $ms^{2}{\cdot}Hz^{-1}$	1044 [600-1874]	2124 [1021-5307]	0.07

Data are median [interquartile range]. BRS_{FD}, baroreflex sensitivity determined by frequency-domain analysis; BRS_{TD}, baroreflex sensitivity determined by a cross-correlation time-domain method; BPV, BP variability; HRV, heart rate variability; LF, low frequency-domain; HF, high frequency-domain.

Association of weight loss, hemodynamics and baroreflex sensitivity

The change in weight was not correlated with changes in MAP (R= -0.21, *p*=0.45), SVR (R= -0.06, *p*=0.84), HR (R= -0.19, *p*=0.50) or CO (R= -0.07, *p*=0.79). The increase in BRS_{TD} correlated inversely with the reduction in HR (R= -0.64, *p*=0.02) and CO (R= -0.61, *p*=0.03) as depicted in figure 2. The change in weight was not correlated with changes in BRS_{TD} (R= 0.27, *p*=0.37).

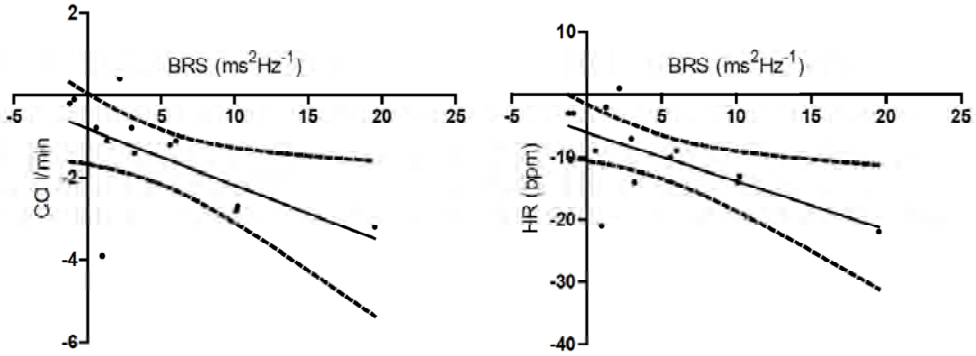

Figure 2. Correlations between changes in baroreflex sensitivity (BRS) and cardiac output (CO, left panel) and between BRS and heart rate (HR, right panel).

DISCUSSION

In the present study we show that the BP reduction following Roux and Y gastric bypass surgery is mediated by a marked reduction in CO and not by changes in SVR. The reduction in CO was associated with an increase in BRS and independent of changes in body weight, suggesting a shift in sympathovagal balance towards increased parasympathetic control. We confirm earlier findings [8,9] by showing that in normotensive and mildly hypertensive morbidly obese females, both office and ambulatory systolic and diastolic BP decreased significantly six weeks after gastric bypass surgery. In addition, we show that next to reduction in peripheral BP, central BP decreased as well, which is in line with a previous study showing a parallel increase in peripheral and central BP with increasing BMI.[26]

Obesity is associated with both structural and functional cardiac changes and characterized by an increase in cardiac workload, increased systolic wall stress and, ultimately, eccentric left ventricular hypertrophy and – dilatation.[16] Gastric bypass surgery has been shown to reduce left ventricular mass and improve left ventricular function after major weight loss.[27–29] However, there is a paucity of data on the short-term effects of bariatric surgery on cardiac function. In contrast, several studies have shown that most of the BP lowering effects following bariatric surgery occur in the first few weeks. In the present study we show that the decrease in BP is explained by a marked reduction in CO. The profound effects of gastric bypass surgery on CO were principally governed by a reduction in HR, but were also mediated by a decrease in SV. In addition, the dP/dt_{max} decreased six weeks after bariatric surgery, suggesting a reduction in left ventricular contractility. Together these hemodynamic changes point towards an early and significant decrease in cardiac workload, which may precede structural changes including a reduction in left ventricular mass. Interestingly, there was no correlation between the amount of weight loss and change in CO nor between weight loss and BP or indices of left ventricular function, while there was a significant (inverse) correlation between changes in BRS and CO. This is in line with previous observations showing that weight loss, either by diet or following gastric bypass surgery, reduces muscle sympathetic nerve activity (MSNA) and increases BRS as a reflection of less sympathetic and more parasympathetic dominance [13–15,30] It has been suggested that this effect may be attributable to a negative energy balance.[31] This is further supported by data showing that after an initial improvement in BRS following a hypocaloric diet, BRS rebounded after four months despite weight maintenance.[32] In addition, a recent publication showed that the sympathoinhibitory effect of gastric bypass surgery was associated with a significant reduction in plasma leptin, [30] pointing to a possible role for leptin in obesity related increase in BP and CO.[33]

In our study the decrease in CO following gastric bypass surgery was accompanied by an increase in SVR. Because SVR is calculated from MAP and CO, the increase in SVR could either be caused by computational variations related to the calculations of MAP and CO or result from a genuine increase related to changes in vasomotor tone following gastric bypass surgery. For example, both insulin and leptin have been shown to cause vasodilation in forearm blood flow studies [34] and decrease shortly after gastric bypass surgery [35,36], providing another explanation for the observed increase in SVR.

The present study addressed BRS directly by frequency- and time domain analysis and found enhanced BRS shortly following bariatric surgery. The reduction in HR and CO, but not in MAP was correlated with an improvement in BRS. Together with the important contribution of HR to the reduction in CO this suggests a change in autonomic balance towards increased parasympathetic HR control. HRV at the respiratory frequency, a measure of parasympathetic activity, is impaired in the severely obese where HRV was shown to improve after gastric bypass surgery.[37] In our study, HRV tended to be higher following surgery, but did not reach statistical significance, possibly due to a lack of power. Ambulatory measurements showed that there was a more pronounced BP decrease during the day compared to night-time. The more pronounced decline in day- vs. night-time ambulatory BP might be related to a more pronounced decrease in SNS activity during the day.[38]

LIMITATIONS

Our study has several limitations. The lack of correlation between multiple parameters may have been subject to a type II error because of the study's limited sample size. We used non-invasive measurements obtained by finger plethysmography to assess MAP and central hemodynamics. Like many hemodynamic assessments, validation studies in this particular population have not been performed. However, the decrease in MAP after bariatric surgery was comparable with the decrease in MAP using the Nexfin device. Furthermore, non-invasive assessment using the pulse contour method (Nexfin CO-trek) has been validated against the thermodilution method and echo-Doppler in various populations under different circumstances, including obese subjects.[21,39,40] In addition, a previous observational study has shown that body weight did not interact with CO using plethysmography (Nexfin) and had an acceptable correlation with CO as measured by echocardiography.[41] Because patients served as their own controls and changes in CO using the pulse contour method adequately track alterations in CO using other methods we assume that the reported differences in CO are valid. We used the maximal ascending slope of the pressure wave, calculated as the maximal value of the first derivative of the pressure pulse, $dP/dt_{max,}$ to estimate changes in left ventricular contractility. Changes in dP/dt_{max} may be subject to changes in preload and vascular properties. However, patients served as their own controls and dP/dt_{max} was studied briefly after bariatric surgery in supine position, thereby minimizing the possibility of the effect of changes in vascular properties and preload respectively. To prove that the change in BRS and CO was not due to variability of the measurements,

we used 24 hour ambulatory BP measurement, which is less sensitive for placebo effects, showing that - in concert with other BP parameters - BP decreased following gastric bypass surgery. Finally, to better appreciate the association between adiposity associated reductions in SNS activity we only studied normotensive and mildly hypertensive women, minimizing the possible confounding effects of BP related changes in SNS activity. Because of the well-established association between hypertension and SNS activity, the effects of gastric bypass surgery on SNS activity in obese women with moderate to severe hypertension may be less unequivocal. In addition, results cannot be extrapolated to men who are, in general, more prone to the development of visceral fat compared to women. Because visceral rather than subcutaneous fat is related to sympathetic activity [42], it is conceivable that the influence of gastric bypass surgery on BRS and CO may be pronounced in men.

CONCLUSIONS

In morbidly obese patients the BP reduction following Roux and Y gastric bypass surgery is explained by a marked decrease in CO and HR. Changes in BRS were associated with changes in CO and HR, but not with weight loss. Our data suggest that the BP decrease following gastric bypass surgery is caused by a shift in autonomic balance towards increased parasympathetic heart rate control that is unrelated to changes in body weight.

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