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Improved Heart Rate Recovery After Marked Weight Loss Induced by Gastric Bypass Surgery: 2 Year Follow Up in the Utah Obesity Study

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Abstract

Background—Obesity is associated with significantly increased cardiovascular mortality that has been attributed, in part, to sympathetic activation. Gastric bypass surgery (GBS) appears to increase long-term survival in the severely obese, but mechanisms responsible for this increase are still being sought. Heart rate (HR) recovery after exercise reflects the balance of cardiac autonomic input from the sympathetic and parasympathetic systems. Blunted HR recovery is a very powerful predictor of increased mortality while enhanced HR recovery portends a good prognosis.

Objectives—To evaluate the effect of marked weight loss achieved via GBS on HR recovery.

Methods—Severely obese patients underwent submaximal exercise testing (80% predicted maximum HR) at baseline and 2 years after GBS (n=153) or nonsurgical treatment (n=188).

Results—Patients in the GBS group lost an average of 100±37 lbs compared to 3±22 lbs in the nonsurgical group (p<0.001, GBS vs. nonsurgical). Resting HR decreased from 73 beats/minute (bpm) to 60 bpm in the GBS group and from 74 bpm to 68 bpm in nonsurgical patients (p<0.001). Heart rate recovery improved by 13 bpm in the GBS group and did not change in the nonsurgical group (p<0.001 GBS vs. nonsurgical). In multivariable analysis, the independent correlates of HR recovery at the 2-year time point were resting HR, treadmill time, age, body mass index and HOMA-IR.

Conclusion—Marked weight loss 2 years after GBS resulted in a significant decrease in resting HR and an enhancement in HR recovery after exercise. These changes are likely attributable to

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improvement in insulin sensitivity and cardiac autonomic balance. Whether and to what extent this contributes to a reduction in cardiovascular mortality with GBS remains to be determined.

Keywords

obesity; exercise; blood pressure; heart rate; autonomic tone; diabetes

BACKGROUND

Overweight and obesity are associated with increased overall mortality, particularly from cardiovascular disease.^{1–4} Gastric bypass surgery (GBS) is becoming an increasingly popular weight loss method for many severely obese people.⁵ In addition to weight loss on the order of 40%,⁶ GBS patients generally see improvements in lipid profile,⁷ glucose tolerance,⁸ blood pressure (BP),⁹ endothelial function¹⁵ and sleep apnea.¹⁰ A few studies have reported improvements in left ventricular function after GBS, although this is less well substantiated.^{11, 12} The duration of the beneficial effects of GBS have not been fully established.^{13, 14} While there are potentially detrimental short and long term effects from bariatric surgery, the benefits appear to outweigh the risks. Recent data indicate significant reductions in total and cause-specific mortality in patients undergoing GBS.¹⁵ The mechanism(s) accounting for the decreased mortality are not fully known. It is also unknown if there are surrogate markers of survival that might help to more quickly evaluate outcomes associated with the expanding use of weight loss surgery.

The decrease in heart rate (HR) during the first 1–2 minutes after exercise termination, referred to as HR recovery, is an indirect measure of the balance between cardiac parasympathetic (vagal) and sympathetic tone.^{16, 17} Faster recovery of HR towards baseline is a marker of higher cardiovascular fitness levels and in large studies, more rapid HR recovery has been associated with better long-term survival.¹⁸ Conversely, reduced HR recovery is a strong indicator of high cardiovascular risk and higher mortality.^{18, 19} It has recently been reported that a short-term (12 week), diet-based weight loss program in overweight men resulted in a significant increase in HR recovery after maximal exercise.²⁰ However, it is unknown whether similar benefits can be attributed to weight loss induced by GBS and what the duration of such benefits might be.

In the current study, we measured HR recovery after exercise at baseline and 2 years after GBS or nonsurgical treatment. We hypothesized that marked weight loss occurring after GBS would be associated with improvement in HR recovery.

METHODS

Study population

The institutional review board of the University of Utah Health Sciences Center approved the protocol. All patients signed a written consent. The rationale and design of the Utah Obesity Study has previously been reported.²¹ From the 1156 initial patients, we studied 341 patients (GBS group, n=153; nonsurgical group, n=188) who had complete cardiovascular datasets at 2-year follow up. Roux-en-Y GBS was done in all surgical patients. The procedure was performed laparoscopically in the vast majority of patients.

Experimental Protocol

Participants were examined at the Huntsman General Clinical Research Center. Data were obtained at the initial visit (Baseline) and again approximately 24 months later (Follow-up).

Serum Chemistry—Following a 12-hour overnight fast, venous blood was drawn for measurement of 20 chemistry variables including glucose, insulin, glycosylated hemoglobin (HbA_{1C}) and a lipid profile. HOMA-IR (an index of insulin resistance) was calculated.²²

Blood Pressure—Blood pressure was measured using automated equipment (Dinamap, Critikon, Tampa, FL). After 5 min of sitting in a quiet room, 3 consecutive BP readings were obtained from the right arm (2 min apart). The mean value was used for analysis.

Submaximal graded exercise test—A modified Bruce treadmill protocol was used. Participants were encouraged to exercise using the handrails only for balance, to 80 % of their age-predicted maximum HR. Maximal tests were not performed because of concerns about safety in severely obese patients. Perceived exertion (6–20 Borg point scale) was recorded at the end of each stage. Blood pressure and HR were recorded during the last 30 seconds of each stage, immediately following, and at one (HR only) two, three and six minutes of recovery. Changes in resting values were calculated as *Follow-up - Baseline*. Recovery values following the exercise bout (HR, systolic BP, diastolic BP) were calculated as *value at minute 2 of recovery - Peak value*. Heart rate recovery was also analyzed at minute 1 of recovery (*HR recovery = HR at minute 1 – Peak HR*). Therefore, a negative value for HR recovery corresponds to a decrease in HR following exercise. Changes in recovery at the 2-year follow-up visit were calculated as *Recovery values at Baseline – Recovery values at Follow-up*. Therefore, a positive value corresponds to a greater recovery at 2 year Follow-up.

Statistical analysis—All values are reported as mean $\pm$ SD. Normally distributed variables were compared using Student's *t*-test. If non-normally distributed, a Mann-Whitney Rank Sum Test was used. Pearson correlations were used to determine associations between linear variables. Multiple linear regression was used to estimate the strength of the associations. Clinically relevant parameters that were significant in the univariable models were included in the initial multivariable model. After the initial model was run, backward stepwise regression analysis was used to successively remove variables from the model that were not statistically significant. Statistical significance was set at $p < 0.05$.

RESULTS

Patient Characteristics

The population was 85% female in the GBS group and 81% female in the nonsurgical group. Age at the beginning of the study was 43 ± 11 years in the GBS group and 48 ± 11 years in the nonsurgical group. Subjects in the GBS group lost an average of 100 ± 37 lbs (range: 0 to 263 lbs). The nonsurgical group lost an average of 3 ± 22 lbs (range: +52 to –130 lbs). Anthropomorphic and blood chemistry variables all improved with the significant weight loss in the GBS group (Table 1).

Baseline hemodynamics and changes in cardiovascular responses to exercise at follow-up

Resting HR (73 vs. 74 bpm) and systolic BP (124 vs. 125 mmHg) were not different in the surgical and nonsurgical groups at baseline (Table 1). Resting HR decreased by 13 ± 13 bpm in the GBS group and by 6 ± 14 bpm in the nonsurgical group ($p < 0.01$ GBS vs. nonsurgical, Table 1). Resting systolic BP exhibited a significant decrease of 8 ± 19 mmHg in the GBS group compared to 2 ± 17 mmHg in the nonsurgical group ($p < 0.01$ GBS vs. nonsurgical, Table 1). Resting diastolic BP did not change from Baseline to Follow-up in either group.

Exercise duration was the same at baseline in the GBS and nonsurgical subjects (917 vs. 917 sec). Exercise time increased by 445 ± 323 sec in GBS subjects while it increased by only 54 ± 273 sec in the nonsurgical group ($p < 0.001$, Table 1). According to protocol, subjects exercised to 80% of their age predicted maximum HR at both Baseline and Follow-up. Therefore, peak HR did not change at Follow-up in either group. However, peak systolic BP during exercise was 17 ± 22 mmHg lower at Follow-up in the GBS group compared to 3 ± 23 mmHg lower in the nonsurgical group ($p < 0.001$, Table 1). Peak diastolic BP during exercise decreased similarly in both groups, 6 ± 11 and 5 ± 10 mmHg, respectively ($p = \text{NS}$).

At baseline, HR recovery was not different between GBS and nonsurgical subjects (-17 vs. -20 bpm, respectively, $p = \text{NS}$). At 2 year follow up compared to baseline, HR recovery improved by 13 ± 15 bpm in the GBS group but did not change in the nonsurgical group at 1 minute ($p < 0.001$) and by 18 ± 15 vs. 3 ± 15 bpm, respectively at 2 minutes ($p < 0.001$, Table 1).

The magnitude of systolic BP recovery was similar in the 2 groups at baseline (-16 vs. -17 mmHg, $p = \text{NS}$). At the 2-year time point, systolic BP recovery decreased slightly in the surgery group (i.e. a lesser absolute degree of recovery) while it increased slightly in the nonsurgical group, -3 ± 20 vs. 5 ± 20 mmHg ($p < 0.001$). This was due to the fact that peak SBP was much lower at peak exercise in the GBS group at follow-up compared to baseline (136 ± 24 mmHg vs. 153 ± 24 mmHg), despite a longer exercise duration at follow-up.

Perceived exertion did not change between baseline and follow up exercise tests ($+0.7 \pm 2.7$ vs. $+0.5 \pm 2.6$) in the GBS and nonsurgical groups, respectively. Of note, this similar level of perceived exertion was in the setting of $\sim 40\%$ longer exercise time in the GBS patients at follow up. Likewise, at any given stage of the treadmill test, HR was significantly lower in the GBS subjects while the nonsurgical group had a much smaller decrease (Figure 1). In other words, GBS patients achieved the same workload at a much lower heart rate. This finding was independent of the decrease in resting HR.

Correlation Between Weight Loss and HR Recovery

To gain insight into potential factors that might be associated with the improvement in HR recovery after GBS, we examined correlations between HR recovery and various anthropomorphic, hemodynamic or biochemical factors. In univariable analysis, there were moderately strong associations between the absolute amount of weight loss or change in BMI and the absolute improvement in HR recovery at 1 minute ($r = 0.35$ and 0.37 , respectively, Figure 2; Table 2). This finding raises the possibility of a direct beneficial effect of weight loss on autonomic tone. However, other factors associated with weight loss, such as resolution of diabetes, could indirectly mediate the advantageous changes in HR recovery. Although it may not be truly linear, the graphical display of the relationship between change in weight and change in HR recovery (Figure 2A and B) for the entire cohort does not suggest a threshold effect, in terms of the amount of weight lost. In multivariable modeling, BMI at visit 2 independently correlated with HR recovery, while surgical status (GBS or nonsurgical groups) did not.

Glucose homeostasis and weight Loss

There were improvements in glucose handling and insulin sensitivity following GBS and the extent of these improvements was strongly related to the magnitude of weight loss (Tables 1 and 2). In multivariable analysis resting HR, treadmill time, age, BMI and HOMA-IR, were each independently associated with HR recovery (Table 3).

Twenty % of our patients were considered diabetic at the baseline visit. Sixteen % of all subjects (similar among both groups) had fasting glucose levels above 120 mg/dl at baseline.

At follow-up, this number dropped from 13% to 4% in the GBS group and from 18% to 11% in the nonsurgical group. At baseline, 17% reported that they were taking diabetes medications (similar among both groups). In the GBS group, those taking medications (either oral agents or insulin) decreased from 17% to 3%. In the nonsurgical group these numbers increased from 17% to 21%. Patients with diabetes at baseline had similar changes in HR recovery at follow-up as those patients without diabetes. In the GBS group, diabetic patients had an improvement of 13.9 bpm in HR recovery vs. 9.0 bpm in the nondiabetic group ($p=0.363$). In comparison, in the nonsurgical group the patients with diabetes had an improvement in HRR of 0.4 bpm and those without diabetes improved by 0.8 bpm ($p=0.801$). In other words, the GBS patients had improvement in HR recovery whether they were initially diabetic or not, while the nonsurgical group had little improvement in HR recovery, whether they were diabetic or not.

Thirty one % of the subjects in this analysis reported taking antihypertensive medication at baseline (no difference between groups). At follow-up this number dropped to 16% in the GBS group, while it increased to 40% in the nonsurgical group. Use of specific classes of antihypertensive agents reported by the overall cohort of patients at baseline and 2 year follow up were as follows: calcium channel blockers (11% vs. 8%); angiotensin converting enzyme inhibitors (14% vs. 14%); angiotensin receptor blockers (8% vs. 11%); other, including beta blockers (8% vs. 8%). HR recovery (absolute value) was lower in subjects with a diagnosis of hypertension at study entry vs. those without hypertension (-15 ± 12 vs. -20 ± 10 , $p = 0.0006$). At 2year follow up, those with a history of hypertension at enrollment continued to have lower HR recovery (-20 ± 12 vs. -27 ± 13 , respectively, $p<0.0001$).

DISCUSSION

Our data show that significant weight loss 2 years after GBS is associated with: 1) markedly improved exercise capacity, 2) a reduction in resting HR and systolic BP and, 3) a marked improvement in HR recovery after exercise. These changes are likely contributed to by a relative enhancement of cardiac vagal tone, with potential contributions from decreased resting sympathetic tone and more rapid sympathetic withdrawal after termination of exercise. The improvements in the physiological parameters are independently related to the amount of weight lost and to decreased insulin resistance. These data support other recent findings suggesting that the sustained weight loss associated with GBS may result in long-term reductions in cardiovascular morbidity and mortality.^{15, 23, 24}

Obesity is associated with increased long-term mortality, mainly from cardiovascular causes.²⁵ Atherosclerosis and heart failure appear to account in part, for the excess mortality in obese individuals. Improved autonomic tone may lead to reductions in both of these disease processes. Such an improvement in autonomic tone might directly contribute to reductions in cardiovascular events since persistent sympathetic stimulation can cause myocyte hypertrophy, myocyte cell death and cardiac fibrosis.²⁶ Indirectly, reductions in sympathetic tone could attenuate the development of heart disease via BP reductions. The lowering of serum lipids and the resolution of insulin resistance following GBS-induced weight loss would be expected to amplify all of the aforementioned cardioprotective effects.^{23, 24}

There is evidence of increased susceptibility to arrhythmias in obese patients.²⁷ Esposito *et al.* suggested that prolonged cardiac repolarization was associated with obesity because of an altered sympathovagal balance.²⁸ If this is true, then it is possible that GBS might reduce arrhythmic events in severely obese subjects through autonomic mechanisms. The possibility that GBS could reduce arrhythmic tendencies is important conceptually, because there are reports that extreme weight loss achieved through some dietary methods has been

associated with sudden cardiac death.²⁹ In the latter case, electrolyte or nutritional imbalances were the likely mechanisms of the arrhythmias. It would be important to know that GBS is not associated with risk factors for sudden cardiac death. Longer follow up will be needed in order to define whether the improved autonomic tone seen after GBS translates into a reduction in clinical event rates.

Interestingly, Billakanty et al described 15 patients who developed syncope related to orthostatic hypotension ~ 5 months after bariatric surgery.³⁰ The authors of this report found evidence that these subjects had autonomic insufficiency as a cause for the new neurological symptoms. These data imply that even seemingly beneficial changes in autonomic function can be pathological if they are excessive or occur too rapidly. We are not aware of such symptoms in our patient population.

Previous studies as well as ours have shown substantial decreases in the frequency of metabolic syndrome, hypertension, diabetes and the use of BP lowering or diabetes medications following GBS.^{31–33} As well, it has also been shown that weight loss via a hypocaloric diet results in a reduction in sympathetic markers.³⁴ Our findings are in keeping with these earlier studies, but our longer duration of follow up indicates a sustained effect after GBS. It is quite likely that both weight loss *and* improved glycemic regulation contribute to the autonomic improvements we found. It is not possible to completely separate the influences of these processes. The multivariable analysis shown in Table 3 suggests that a lower BMI and a lower HOMA-IR at the time of the 2-year follow up each have independent associations with improvement in HR recovery.

Lifestyle modification usually includes changes in diet and increased exercise. Increases in parasympathetic and decreases in sympathetic nerve activity, and improved HR recovery have been seen after weight loss achieved by dieting in obese individuals.^{20, 35, 36} Similarly, it is well known that exercise training is associated with increased resting vagal tone and more rapid HRR after exercise.^{37, 38} Unfortunately, very few severely obese patients are able to maintain significant weight loss through lifestyle modification. Among the various surgical procedures practiced today, Roux-en-Y GBS is still the most common. In the Swedish Obesity Study, GBS was associated with significantly more initial weight loss, and more sustained weight loss than gastric banding alone.³⁹ Moreover, patients undergoing gastric banding procedures did not maintain reductions in BP at 10 year follow up. Prior to the present study, it was unclear whether weight loss achieved via Roux-en-Y GBS resulted in autonomic benefits similar to those achieved with diet and exercise. Our findings now extend the autonomic benefits of weight loss to patients undergoing this form of bariatric surgery.

Other factors such as sex hormone levels are significantly affected by adiposity and weight loss.⁴⁰ Although we do not have measurements of these hormones in the majority of our patients, the anticipated direction of change with marked weight loss would be a relative increase in circulating levels of male vs. female sex hormones. Previous work suggests that males have higher cardiac sympathetic tone whereas females have higher parasympathetic cardiac autonomic tone.⁴¹ If changes in sex hormones were a major factor contributing to the observed changes in HR recovery, marked weight loss would likely reduce rather than increase HR recovery when compared to baseline. Seventy seven % of female subjects who provided data on menstrual status at baseline were premenopausal.

LIMITATIONS

Multiple variables changed following GBS. Thus, it is not possible to define a single mechanism responsible for the main outcome of improved HR recovery. Regardless of the exact mechanism(s), our data strongly suggest that bariatric surgery may improve the

conditions associated with high cardiovascular mortality in obesity. This would be an extremely important outcome given the very rapid rise in the prevalence of obesity and the increasing use of surgical weight loss procedures. Another issue is that our population was 83% female. In our small percentage of male subjects we saw similar improvements in HR recovery as were seen in the women. Importantly, severe obesity is twice as prevalent in females as in males and women are often underrepresented in cardiovascular studies. It would also be very informative to collect direct measures of parasympathetic and sympathetic activity such as serum catecholamines, microneurography or even heart rate variability. Those measurements are not available from this dataset and in some cases are quite difficult to acquire in severely obese subjects. We also do not have 24 hour Holter monitoring in our subjects. Exercise was not specifically prescribed or monitored in either group. While it is likely that some patients who lost weight did more exercise than those who did not lose weight, we cannot quantitatively assess the effects of exercise on our outcome measures. Follow-up on these patients has not been long enough to study potential changes in clinical arrhythmias or survival. Despite these limitations, weight loss with GBS showed very promising results and further studies of mechanisms and outcomes are clearly warranted.

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Figure 1.

Changes in HR at each stage of the exercise treadmill test between the baseline and the follow up visit. GBS patients had a significantly greater drop in heart rate at each stage than the nonsurgical group. Peak HRs were similar between the 2 visits since tests were terminated at 80% maximum HR. However, at 2 year follow-up, GBS patients exercised ~ 40% longer to achieve the same peak HR.

Figure 2.

A) Correlation between the amount of weight loss and the change in HR recovery at 2-year follow up. B) Change in absolute HR recovery based on quartiles of weight change (absolute values) for the entire group. C) Change in HR recovery based on quartiles of weight change in the nonsurgical group: +52 to +20 lbs (n=20), +19 to -12 lbs (n=122), -13 to -44 lbs (n=38), -45 to -76 lbs (n=7). D) Change in HR recovery based on quartiles of weight change in GBS: 0 to -46 lbs (n=7), -47 to -92 lbs (n=61), -93 to -138 lbs (n=62), -139 to -184 lbs (n=22).

TABLE 1

	GBS (n=153)			Nonsurgical (n=188)			p-value GBS vs. Nonsurgical
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	
Age (yrs)	43±11			48±11			
Sex (% female)	84%			82%			
Height (in)	66±6			66±6			
Weight (lbs)	292±63	193±51	-100	268±48	265±51	-3	<0.001
BMI (kg/m ²)	47±8	31±7	-16	43±7	43±7	0	<0.001
Waist (cm)	135±21	102±20	-33	130±17	129±18	-1	<0.001
Hip (cm)	142±18	113±18	-28	135±16	136±17	2	<0.001
Resting HR	73±14	60±12	-13	74±13	68±13	-6	<0.001
Resting SBP	124±21	115±20	-8	125±19	123±22	-2	<0.001
Resting DBP	69±11	69±11	0	71±11	70±13	-1	0.77
Peak HR	137±17	136±17	-2	136±16	134±16	-2	0.64
Peak SBP	153±24	136±24	-17	158±26	155±27	-3	<0.001
Peak DBP	85±11	80±10	-6	86±11	82±11	-4	0.15
HR Recovery (1 m)	-17±10	-30±14	-	-20±12	-20±11	0	<0.001
HR Recovery (2 m)	-39±14	-56±15	18	-40±15	-43±14	3	<0.001
SBP Recovery (2 m)	-16±16	-12±13	-3	-17±17	-22±17	5	<0.001
DBP Recovery (2 m)	-8±8	-5±5	-2	-7±7	-5±6	-2	0.99
Treadmill Time (sec)	917±358	1,362±322	445	917±347	972±347	54	<0.001
Glucose (mg/dL)	102±26	83±23	-19	107±37	100±31	-7	<0.001
Total Cholesterol (mg/dL)	187±37	163±34	-25	188±41	188±42	0	<0.001
Triglyceride (mg/dL)	185±81	106±54	-79	178±93	164±84	-14	<0.001
HDL (mg/dL)	47±11	56±14	9	47±12	44±10	-3	<0.001
LDL (mg/dL)	108±28	92±29	-17	108±30	115±32	8	<0.001
Plasma Insulin (U/ml)	20±15	6±6	-14	16±16	17±11	2	<0.001
HOMA-IR	5.0±3.8	1.2±1.3	-3.8	4.0±3.9	4.1±2.7	0.2	<0.001
HbA _{1c} (%)	5.9±1.1	5.6±0.8	-0.3	5.8±1.1	6.1±0.9	0.3	<0.001

HR = heart rate (beats/min); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 2

Correlates of 1-minute HR recovery at 2-year follow up in univariable analysis

Variable	t-statistic	r	p
Weight (kg)	−8.7	−0.34	<0.0001
Δ weight	6.9	0.35	<0.0001
BMI (kg/m ²)	−7.4	−0.37	<0.0001
Δ BMI (kg/m ²)	7.3	0.37	<0.0001
Treadmill time (sec)	8.5	0.42	<0.0001
SBP (mmHg)	−3.8	−0.204	0.0002
DBP (mmHg)	−1.13	−0.06	0.26
Resting Heart Rate (bpm)	−5.2	−0.27	<0.0001
Glucose (mg/dl)	−4.8	−0.25	<0.0001
Insulin (IU/ml)	−5.9	−0.31	<0.0001
HDL (mg/dl)	4.2	0.23	<0.0001
HbA1c (%)	−4.4	−0.26	<0.0001
HOMA-IR	−6.2	−0.32	<0.0001

Positive values indicate positive correlation with larger absolute value of HR recovery.

Table 3

Factors associated with HR recovery at 2-years in a multivariable model

Variable	t-statistic	Std Beta	p
Resting heart rate (bpm)	-2.87	-0.15	0.004
Treadmill time (s)	2.74	0.19	0.006
Age (yrs)	-2.57	-0.14	0.01
Sex (F)	-2.57	-0.13	0.01
HOMA-IR	-1.96	-0.11	0.05
BMI (kg/m ²)	-1.95	-0.13	0.05

Positive values indicate positive correlation with larger absolute value of HR recovery.