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Vascular Risk Factors

Exercise and Weight Loss Improve Exercise Capacity Independent of Cardiac Function in Metabolic Syndrome

Anand Chockalingam, MD, Melissa A. Linden, MA, Marc Del Rosario, MD, Gurushankar Govindarajan, MD, Kevin C. Dellsperger, MD, PhD, and Tom R. Thomas, PhD

Hypertension, diabetes and obesity cause cardiac diastolic dysfunction (DD) which could reduce exercise capacity. Our aim was to determine if 10% weight loss by exercise at 60% VO$_{2\text{max}}$ five days/week (~375 kcal/session) and caloric restriction (~600 kcal/d) over 6 months improves exercise capacity and DD in Metabolic Syndrome (MetS). Eighteen subjects (40 ± 1y, women = 6, BMI = 33.5 ± 1.0 kg/m$^2$) successfully completed the study. Maximal treadmill stress echocardiography was performed at baseline and post weight loss to determine VO$_{2\text{max}}$, resting and stress DD as the ratio of peak early diastolic mitral inflow velocity (E) to tissue Doppler early diastolic annular decent (E'). After weight loss (mean = 9.5 ± 0.2%), all metabolic parameters improved. Resting and stress E/E' values remained normal before and after weight loss. Exercise intolerance is likely due to general deconditioning and not cardiac dysfunction in early MetS as VO$_{2\text{max}}$ increases significantly with lifestyle while cardiac function remains unchanged.

Keywords: metabolic syndrome; diastolic function; weight loss; exercise capacity; lifestyle changes; E/E'

Introduction

Heart failure with normal ejection fraction (HFNEF) is increasingly recognized, accounting for about 50% of all heart failure hospitalizations in the United States. Long-term outcomes are similar to those with systolic heart failure. Although the etiology is likely multifactorial, myocardial hypertrophy, fibrosis, and reduced compliance appear to cause left ventricular (LV) diastolic dysfunction (DD)-related filling pressure elevations seen in most HFNEF participants.

Morbid obesity and diabetes, like hypertension, can directly and independently cause LV hypertrophy and DD. Recent reports correlated exercise capacity with Doppler echocardiography-derived diastolic function parameters. We recently reported the absence of cardiac dysfunction in sedentary metabolic syndrome (MetS) participants. Nevertheless, Doppler-measured DD still correlated with exercise capacity in MetS.

We hypothesized that significant weight loss in MetS through diet and exercise would improve cardiac function along with exercise capacity, as measured by maximal oxygen consumption (VO$_{2\text{max}}$).

Methods

We screened 60 participants who were overweight to class II obesity (body mass index [BMI] 25.0-39.9 kg/m$^2$) and sedentary, defined as not meeting the Surgeon General’s recommendations, which is
for more than 150 min/week of physical activity (Table 1). Of them, 36 fulfilled at least 2 of 5 criteria for the MetS as determined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III): elevated blood pressure ([BP] >130/85 mm Hg), elevated plasma triglyceride concentrations (>150 mg/dL), elevated fasting blood glucose (>100 mg/dL), elevated waist circumference (>88 cm in females, >102 cm in males), and reduced high-density lipoprotein cholesterol (HDL-C) concentrations (<50 mg/dL in females, <40 mg/dL in males). Participants were excluded if they had a fasting blood glucose >125 mg/dL or known cardiovascular disease to limit confounding effects of diabetes and long-standing hypertension. Inclusion required at least 2 of 5 metabolic criteria. All participants were informed of risks and benefits of participation and signed a written consent approved by our Institutional Review Board. Participants were weightstable (body weight change of less than ±5%) and had not participated in a formal diet program within 3 months prior to the start of the study. Participants were all nonsmokers and not taking antihypertensive or weight-altering medications, including over-the-counter supplements. These participants were a cohort of volunteers from a larger long-term study on the effect of lifestyle on cardiometabolic risk.

### Treadmill Protocol

Using the standard Bruce treadmill protocol, stress testing was conducted on all participants under close physician supervision. All participants were exercised to volitional fatigue. Heart rate, BP, and electrocardiogram (ECG) were monitored continuously. Reason for treadmill termination was documented and VO2max measured using the Parvo Medics TrueOne 2400 metabolic measurement system (Parvo Medics Inc, Sandy, UT) and a Hans Rudolph 2-way nonrebreathing valve (Hans Rudolph Inc, Kansas City, MO). The highest oxygen consumption value obtained during the test was considered the participant’s VO2max. In order for this value to be considered a valid measure, at least 2 of the following criteria were met: respiratory exchange ratio >1.15, a plateau in oxygen consumption (<2 mL/kg per minute increase in VO2 between progressive stages), and maximal heart rate within 10 beats of age-predicted maximal heart rate (maximal heart rate = 220 – age).

### Stress Echocardiography

Using a Vivid i portable echocardiographic unit (GE Healthcare, Waukesha, WI), 2-dimensional (2D) imaging was obtained using standard stress echocardiography protocol. Patients with significant structural heart disease manifested as cardiac chamber enlargement, dysfunction, valve disease, and significant pulmonary hypertension were excluded. All participants in our study group had normal cardiac function. Baseline wall motion analysis was performed using the apical 4- and 2-chamber views and parasternal long and short axis views. Prior to exercise, pulse Doppler mitral inflow velocities as well as medial and lateral annular tissue Doppler imaging (TDI) velocities were obtained using the apical 4-chamber view.

Repeat echocardiographic imaging with 2D imaging to evaluate global LV function and wall motion was performed within the first 60 seconds of termination of the maximal exercise. Pulse Doppler mitral inflow velocities and mitral annular TDI velocities were obtained from the apical 4-chamber view over the next few minutes after the waveforms separated adequately. Mitral regurgitation and pulmonary artery systolic pressures (by tricuspid regurgitation peak velocity + right atrium [RA] pressure) were estimated postexercise when present.

### Diastolic Function Measurements

For each patient, the mean value of the pulse wave early diastolic mitral inflow velocity (E) was obtained over 5 cardiac cycles at the level of the mitral valve.
tip from the apical 4-chamber view. Using TDI, the early diastolic peak of the annular descent from both the medial and the lateral walls was measured over 5 cycles. E’ represents the average of medial and lateral early diastolic mitral annular TDI descent. Left ventricular–filling pressure was indirectly estimated from E/ E’,22–25 Postexercise or stress E/E’ was measured after completion of exercise in the supine position. Rest and stress E/E’ measurements below 8 to 10 are considered normal and over 13 to 15 have been correlated with reduced exercise capacity below 8 metabolic equivalents (METs).16-18

Weight-Loss Program
Exercise regimen consisted of closely supervised treadmill walking or jogging at 60% of VO2max 5 times a week for 45 minutes per session, targeting 375 kcal/session. Individually prescribed balanced diet was aimed at achieving and maintaining a negative 600 kcal/day calorie restriction. Adherence was closely monitored and encouraged targeting 10% weight loss over the 6-month study period.

Post Weight Loss Testing
All participants who successfully achieved the target of 10% body weight loss underwent a repeat maximal tolerance stress test to determine VO2max treadmill time, and METs using the same protocol as the baseline test. Echocardiography with resting and stress diastolic function parameters was again obtained.

Statistical Analysis
One-way analysis of variance (ANOVA) with repeated measures (time) was used to determine changes in parameters of metabolic health, exercise capacity, and DD after 10% body weight loss with diet and exercise training. Pearson product correlations were used to determine relationships between resting E/E’ and VO2max and postexercise E/E’ and VO2max at both baseline and after weight loss with diet and exercise training. Statistical analysis was done using SPSS (SPSS/11.0; SPSS, Chicago, IL).

Results
Eighteen overweight-obese (mean BMI = 33.5 ± 1.0 kg/m²) participants aged 40 ± 1 years successfully completed the study by losing 10% of their baseline weight. Among the 18 participants, 12 met 3 criteria of MetS. Exercise compliance in the group that completed the weight-loss protocol was 96%. Weight loss (mean 9.5 ± 0.2% of baseline body weight) and exercise training resulted in all the following tested metabolic parameters changing significantly (P < .05) in the healthier direction: VO2max, waist circumference, systolic and diastolic BP, blood glucose, insulin resistance, and cholesterol (Table 1).

Systolic and diastolic cardiac function was unaffected in this group despite poor baseline VO2max. Resting and stress E/E’ values remained within the normal range before and after weight loss and did not correlate with hemodynamic parameters, loading conditions, or VO2max.

The average treadmill time was 8.34 ± 0.28 minutes at baseline. The VO2max achieved at baseline was 29.1 ± 1.1 mL/kg per minute at a mean 8.5 ± 0.3 METs. The reason for terminating treadmill stress was volitional exhaustion, shortness of breath, or nonspecific leg pains. After completion of weight loss–exercise program, the Bruce protocol treadmill time increased to 9.83 ± 0.28 minutes and VO2max to 35.9 ± 1.3 mL/kg per minute (Table 2). Systolic cardiac function was normal at both time points. E/E’ was within normal range in all participants at baseline (resting 7.24 ± 0.56 and stress 6.50 ± 0.44) and did not change significantly post weight loss (resting 7.08 ± 0.26 and stress 7.49 ± 0.23). No significant correlation was evident between resting and exercise-related systolic or diastolic BPs

Table 2. Treadmill Exercise and Echocardiographic Variables at Baseline and Post Weight Loss (n = 18)a

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Bruce protocol (minutes)</td>
<td>8.33 ± 0.3</td>
<td>9.83 ± 0.3b</td>
</tr>
<tr>
<td>METs</td>
<td>8.5 ± 0.3</td>
<td>10.3 ± 0.4b</td>
</tr>
<tr>
<td>VO2max (L/min)</td>
<td>3.1 ± 0.2</td>
<td>3.4 ± 0.2b</td>
</tr>
<tr>
<td>VO2max (mL/kg per minute)</td>
<td>29.5 ± 1.1</td>
<td>35.9 ± 1.3b</td>
</tr>
<tr>
<td>Maximal heart rate (bpm)</td>
<td>181 ± 2</td>
<td>178 ± 3</td>
</tr>
<tr>
<td>Resting E/E’</td>
<td>7.2 ± 0.6</td>
<td>7.1 ± 0.2</td>
</tr>
<tr>
<td>Exercise E/E’</td>
<td>6.5 ± 0.4</td>
<td>7.5 ± 0.2b</td>
</tr>
</tbody>
</table>

NOTES: bpm = beats per minute; E/E’ = the ratio of peak early diastolic mitral inflow velocity (E) to tissue Doppler early diastolic annular descent (E’); METs = metabolic equivalents; VO2max = maximal oxygen consumption.

a Values are expressed as means ± SE.
b Post weight loss is significantly different from baseline (P < .05).
and E/E' measurements at baseline and following weight loss. Neither resting nor stress E/E' correlated significantly with $V_0_{2max}$ at baseline and following weight loss (Table 3). No significant pulmonary hypertension or stress-related mitral regurgitation was detected at baseline or after weight loss.

**Discussion**

Recent literature suggests that patients with higher poststress E/E' levels demonstrated lower peak $V_0_{2max}$. Significant inverse correlation exists between postexercise Doppler derived indices of DD and exercise capacity. E/E' below 8 is considered normal and values over 15 correspond with elevated LV-filling pressures. Thus, estimation of E/E' during stress testing now offers a novel tool to quantify DD. Our study demonstrated that the limited exercise capacity of sedentary MetS participants was unrelated to cardiac function even when tested with these new “stress diastolic function” echo parameters.

**Metabolic Syndrome and Exercise Tolerance**

Sedentary lifestyle and lack of conditioning is likely responsible for reduced exercise capacity in the majority of obese MetS individuals. Left ventricular hypertrophy and diastolic filling abnormalities can develop in long-standing hypertension; however, patients with long-standing hypertension were excluded from our study. There is new evidence to suggest that diabetes and morbid obesity can independently cause similar cardiac stiffening and hypertrophy without hypertension. Metabolic syndrome being a clustering of these factors would be expected to result in similar DD and clinically could manifest as dyspnea during exercise. Our experience suggests that cardiac function is normal and most of the reduction in exercise capacity is related to deconditioning.

**Stress Diastology in MetS**

We routinely use treadmill stress echocardiography for the evaluation of cardiac contribution toward dyspnea in obese MetS patients. Traditionally, we assess exercise time, ECG, and clinical parameters as well as stress LV systolic function to evaluate for ischemia. Given the prevalence of sleep apnea and lung disease, we also routinely check for pulmonary pressures using tricuspid regurgitation Doppler postexercise. In a recent series, the occurrence of “occult DD” that requires stress testing to manifest elevated E/E' was estimated at about 10% among dyspneic participants. We have not demonstrated significant resting or stress diastolic abnormalities in our small cohort of MetS participants despite their limited exercise tolerance. The relatively younger age, short duration of MetS characteristics, and nonspecific deconditioning might account for the lack of diastolic function abnormalities. Nevertheless, this study shows that treadmill stress echocardiography would be a suitable tool to evaluate dyspnea in MetS as it can test for ischemia (LV systolic function and regional wall motion) and also evaluate diastolic function (stress E/E', LA size, and pulmonary artery pressures).

**Lifestyle and Weight Loss in MetS**

Thus far, trials with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and angiotensin-receptor blockers have not shown improvement in HFNEF. Onset of clinical heart failure might represent advanced irreversible myocardial changes not amenable to medications. Prior reports have consistently demonstrated significant improvements in cardiometabolic risk factors with exercise and weight reduction. Thus, we hoped to identify early
preclinical DD in MetS that may improve with lifestyle and control of MetS risk factors. Our cohort likely had early MetS, and the duration of risk factors may be too short to cause significant alterations in cardiac function despite the impairment in exercise capacity. Improvements in lifestyle are nevertheless crucial in managing this complex problem.

Limitations

We studied a well-characterized group of MetS participants that successfully reached the 10% weight loss end point. However, at baseline, our group was probably “too healthy” or too early in the natural progression of MetS to manifest DD. We did not perform invasive cardiac pressure and output measurements. Effect of lifestyle on DD would be evident if we had preselected MetS participants with evident DD.

Conclusions

We conclude that poor exercise tolerance was likely related to general deconditioning and body habitus in a relatively normal younger population of MetS patients. Our findings of improved VO2max and cardiometabolic risk factors with 6 months of exercise, diet, and 10% weight loss were not associated with improvements in cardiac function at rest or with stress.

Acknowledgments

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References


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