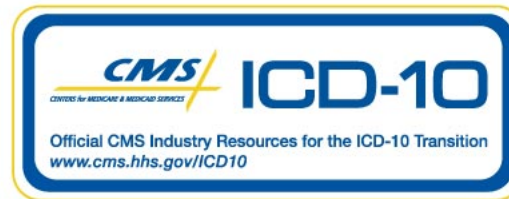


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**Diabetes Lowers Aerobic Capacity in Heart Failure**

Amit S. Tibb, Pierre V. Ennezat, Jennifer A. Chen, Ali Haider, Susheel Gundewar, Vlad Cotarlan, Vimla S. Aggarwal, Ashok Talreja, and Thierry H. Le Jemtel  
*J. Am. Coll. Cardiol.* 2005;46:930-931; originally published online Aug 9, 2005;  
doi:10.1016/j.jacc.2005.06.001

**This information is current as of February 10, 2012**

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**JACC**

*JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY*



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#### Diabetes Lowers Aerobic Capacity in Heart Failure

**To the Editor:** Patients with chronic heart failure (CHF) due to left ventricular (LV) systolic dysfunction develop skeletal muscle alterations that contribute to lower peak aerobic capacity (1). Patients with type 2 diabetes develop skeletal muscle alterations similar to those of patients with CHF (2). To test the hypothesis that diabetes may further reduce peak aerobic capacity in patients with CHF, we prospectively measured peak oxygen uptake (peak  $\text{VO}_2$ ) in 156 diabetic and nondiabetic patients with CHF who were matched for age and gender.

A total of 156 patients met inclusion/exclusion criteria and agreed to participate in the study. We first identified 204 patients with CHF and diabetes among the 689 patients with LV ejection fraction  $<40\%$  in our CHF clinic and then attempted to match these 204 diabetic patients for age and gender to the 485 remaining nondiabetic patients. We found age and gender matches for 106 of the 204 patients. Informed consent and complete data were obtained in 78 of the 106 matched patients. Inclusion criteria included: steady clinical state, ability to perform a maximal exercise test, and therapy consistent with current CHF guidelines. Exclusion criteria were: exertional angina or arrhythmias; systolic or diastolic blood pressure  $>160$  and  $90$  mm Hg, respectively; joint, pulmonary, or peripheral arterial disease; participation in a training program; and active tobacco use. Glycosylated hemoglobin was measured in all patients. They had all undergone coronary angiography. Chronic kidney disease was defined by a creatinine clearance  $<50$  ml/min (3). All patients were familiar with exercise testing and measurement of expired gas.

Patients who met inclusion and exclusion criteria underwent evaluation of baseline physical activity. Plasma B-type natriuretic peptide (BNP) level and peak  $\text{VO}_2$  were determined within one week of evaluation of physical activity. The average number of daily steps was used to quantify baseline physical activity (4). It was recorded daily and averaged over seven consecutive days. Ejection fraction was assessed by echocardiography. Plasma levels of BNP were measured using the triage immunoassay (Biosite Inc., San Diego, California). Peak  $\text{VO}_2$  was measured during a symptom-limited treadmill exercise test. Patients who discontinued exercising for other than shortness of breath and fatigue or did not reach a respiratory exchange ratio  $>1.0$  were excluded. Peak  $\text{VO}_2$  was compared in diabetics and nondiabetics using the  $t$  test for two independent samples. Multiple linear regression analysis was performed to assess the effect of diabetes on peak  $\text{VO}_2$  controlling for hypertension, coronary artery disease (CAD), chronic kidney disease, BNP plasma level, LV ejection fraction, physical activity, and glycosylated hemoglobin. We aimed to have a minimum of 15 patients for each parameter that we anticipated to include in our regression model.

Baseline characteristics and medications are summarized in Table 1. Hypertension and CAD were more prevalent in diabetics than in nondiabetics. Plasma BNP level, ejection fraction, body mass index, prevalence of chronic kidney disease, number of daily steps, and therapeutic regimen (except for aspirin) were similar in

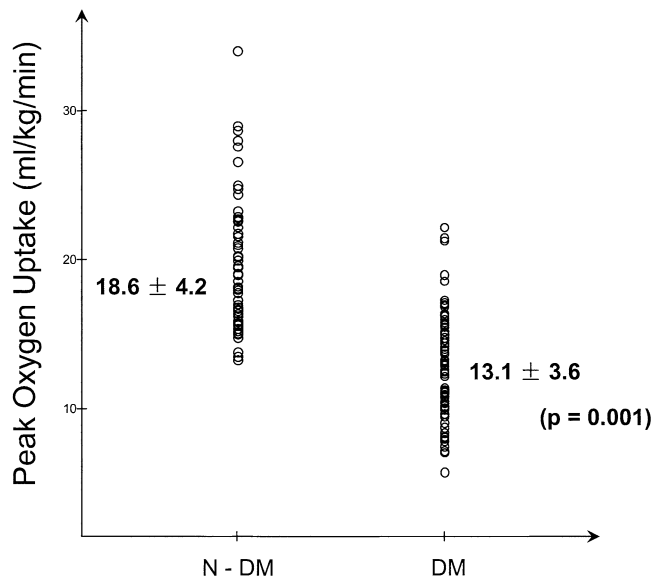
diabetics and nondiabetics. Peak  $\text{VO}_2$  was substantially lower in diabetic than in nondiabetic patients:  $13.1$  (SD  $3.6$ ) versus  $18.9$  (SD  $4.2$ ) ml/kg/min ( $p = 0.001$ ) (Fig. 1). Peak heart rate and ventilatory threshold were similar in diabetics and nondiabetics. The difference in peak  $\text{VO}_2$  between diabetics and nondiabetics was  $5.5$  ml/kg/min ( $p < 0.001$ ) after controlling for baseline characteristics.

Our data extend the findings of Guazzi et al. (5) to a larger and more controlled patient population. Our data also provide the first evidence that diabetes is an independent determinant of peak  $\text{VO}_2$  in patients with CHF. Guazzi et al. (5) studied 40 diabetic and nondiabetic patients with CHF. Half of the patients were receiving angiotensin-converting enzyme inhibitors, and none were receiving beta-adrenergic blockade. Guazzi et al. (5) did not measure baseline physical activity nor consider whether differences in comorbid conditions could account for the lower peak  $\text{VO}_2$  of diabetic patients. The difference in peak  $\text{VO}_2$  was lower in the Guazzi et al. (5) study than in ours:  $3.0$  versus  $5.5$  ml/kg/min. Tighter diabetes control with aggressive insulin therapy may have

**Table 1.** Characteristics and Medications

	Diabetic n = 78	Nondiabetic n = 78	Statistical Significance p Value
Age (yrs)	61.6 ± 9.7	61.6 ± 9.7	—
Men (%)	74.4	74.4	—
Physical activity (number of steps)	8,068 ± 4,169	8,012 ± 4,051	0.89
BMI (kg/m <sup>2</sup> )	27.4 ± 2.3	26.9 ± 2.7	0.58
LVEF (%)	32.0 ± 13.0	33.5 ± 10.0	0.26
Hgb (g/dl)	13.2 ± 1.6	13.2 ± 1.9	0.96
BNP level (pg/ml)	194.0 ± 366.7	109.5 ± 209.7	0.34
HgbA1c (%)	7.4 ± 1.1	5.0 ± 0.1	0.00
CAD (%)	70.5	52.4	0.01
HTN (%)	78.2	61.9	0.02
History of tobacco use (%)	51.3	53.2	0.79
CKD (%)	35.9	32.1	0.73
Atrial fibrillation (%)	8.9	10.2	0.89
Insulin (%)	66.7	—	—
Sulfonylureas (%)	57.7	—	—
Metformin (%)	35.1	—	—
Pioglitazones (%)	11.5	—	—
Metoprolol or carvedilol (%)	92.3	86.5	0.20
ACE inhibitor or ARB (%)	92.3	88.1	0.34
Digoxin (%)	52.6	42.8	0.47
Aspirin (%)	71.8	57.1	0.03
Statin (%)	70.9	57.5	0.08
Loop diuretics (%)	85.9	83.3	0.69

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CKD = chronic kidney disease; Hgb = hemoglobin; HgbA1c = glycosylated hemoglobin; HTN = hypertension; LVEF = left ventricular ejection fraction.



**Figure 1.** Individual peak oxygen uptake (peak  $\text{VO}_2$ ) values in diabetic (DM) and nondiabetic (N-DM) patients with chronic heart failure due to left ventricular systolic dysfunction. Mean peak  $\text{VO}_2$  is significantly lower in DM than in N-DM patients.

contributed to the smaller difference in peak  $\text{VO}_2$  between diabetics and nondiabetics in the Guazzi et al. (5) study. Glycosylated hemoglobin was <7% in every one of the Guazzi et al. (5) patients, whereas it averaged 7.5% in our patients. Insulin therapy improves peak  $\text{VO}_2$  in patients with diabetes and CHF (6,7). Diabetes is associated with cardiac, vascular, metabolic, and skeletal muscle alterations that all tend to reduce peak  $\text{VO}_2$  (8). High-energy phosphate metabolism is impaired in skeletal muscles from patients with diabetes in the absence of CAD or LV dysfunction (2). Phosphocreatinine loss, pH decline, and deoxygenation occur sooner in exercising skeletal muscles of diabetics than in controls. Alterations in energy metabolism contribute to reduce peak aerobic capacity in CHF (9,10). The coexistence of diabetes and CHF may further alter skeletal muscle energy metabolism and reduce peak aerobic capacity. A major limitation of our study is the absence of longitudinal data with tighter diabetes control.

In summary, diabetes negatively impacts on and is an independent determinant of peak aerobic capacity in patients with CHF. Diabetes needs to be taken into consideration when evaluating functional capacity in patients with CHF.

### Left Ventricular Wall Motion Abnormalities Induced by Squatting: A New Echocardiographic Stress Test for the Diagnosis of Coronary Artery Disease

**To the Editor:** Stress echocardiography is useful for diagnosing coronary artery disease (CAD) (1,2). Expense, potential for complications, and the time factor are potential disadvantages of these techniques. Thus, there is a need for a simple, inexpensive, rapid, and safe echocardiographic stress test.

Squatting increases left ventricular afterload and preload (3-5). This study tested the hypothesis that squatting will produce left ventricular wall motion abnormalities (WMA) in patients with CAD.

The study population consisted of 15 normal male subjects (group 1) (age range 34 to 75 years, mean 57 years) and 42 male

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doi:10.1016/j.jacc.2005.06.001

Please note: Dr. Le Jemtel is on the Speaker's Bureau of Scios, Glaxo SmithKline, and Astra Zeneca, and does consultation work for Novartis.

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patients (mean age 63 years, range 31 to 84 years) who had coronary angiography (group 2). The institutional committee on human research approved the study protocol. Informed consent was obtained from all subjects.

The standing (3 min of quiet standing) heart rate and blood pressure were recorded. Parasternal long- and short-axis and apical four-, two-, and three-chamber views were obtained in the standing position. The subjects were asked to squat, for 2 min. Blood pressure, heart rate, and echocardiograms were recorded. The echocardiogram was repeated after standing.

A 16-segment model was used for analysis of echocardiographic

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**This information is current as of February 10, 2012**

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