Insulin Ameliorates Exercise Ventilatory Efficiency and Oxygen Uptake in Patients With Heart Failure–Type 2 Diabetes Comorbidity

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OBJECTIVES
This study sought to test whether insulin improves exercise ventilatory efficiency (VE/VCO₂ slope) and oxygen uptake at peak exercise (peak VO₂) in patients with type 2 diabetes–heart failure (HF) comorbidity.

BACKGROUND
In type 2 diabetes–HF comorbidity, depression of alveolar–capillary diffusion (DLCO) correlates with deterioration of exercise VE/VCO₂ slope and peak VO₂. Insulin potentiates DLCO in these patients.

METHODS
Exercise ventilatory efficiency and peak VO₂ (cycle ergometry ramp protocol), as well as DLCO at rest and its subdivisions (membrane conductance [DM] and pulmonary capillary blood volume [VC]) were assessed in 18 patients with type 2 diabetes–HF comorbidity at baseline and after 50 ml of saline or regular insulin (10 IU), or saline, was infused on consecutive days, according to a random crossover design. Glycemia was kept at pre-insulin level for the experiment duration.

RESULTS
Baseline DLCO, DM, peak VO₂, and VE/VCO₂ slope were compromised in these patients. At measurements performed in the 60 min after infusions, compared with at baseline, saline was ineffective, whereas insulin augmented peak VO₂ (+13.5%) and lowered VE/VCO₂ slope (+18%), and also increased time to anaerobic threshold (+29.4%), maximal O₂ pulse (+12.3%), aerobic efficiency (+21.2%), DLCO (+12.5%), and DM (+21.6%), despite a reduction in VC (−16.3%); insulin did not vary cardiac index and ejection fraction at rest. Changes in peak VO₂ and VE/VCO₂ slope (r = 0.67, p = 0.002; r = −0.73, p < 0.001, respectively) correlated with those in DLCO. These responses were unrelated to glycohemoglobin and baseline fasting blood sugar. They were persistent at 6 h after insulin infusion, and were undetectable at 24 h.

CONCLUSIONS
In diabetes–HF comorbidity, insulin causes a prolonged improvement in physical performance through activation of multiple factors, among which facilitation of gas conductance seems to be predominant. (J Am Coll Cardiol 2003;42:1044–50) © 2003 by the American College of Cardiology Foundation

Diabetes mellitus, as a comorbid disease, frequently confounds heart failure (HF) and adds significantly to its overall morbidity (1–3). Poor glycemic control is associated with an increased risk of HF in type 2 diabetes (4,5); blood glucose control substantially reduces the risk of vascular complications (4) and improves endothelial function (6). At the lung level, the alveolar–capillary membrane becomes a target structure of the coexisting diseases; left ventricular dysfunction causes a hydrostatic stress on the membrane (7), and diabetes alters the alveolar and pulmonary capillary basal laminae (8), resulting in a synergistic depression of the membrane conductance and gas exchange (9). This alteration correlates with a joint adverse influence of these diseases on exercise ventilatory efficiency and peak exercise oxygen uptake (peak VO₂) (9). In the setting of comorbidity, insulin may be beneficial. The hormone, in fact, reduces mortality in diabetes after acute myocardial infarction (10), improves hemodynamics in HF without diabetes (11), attenuates impedance to alveolar–capillary interface gas transfer in patients with diabetes (12) and even more in case of comorbidity (13). There is no report concerning an influence of insulin on exercise ventilatory efficiency and oxygen uptake (VO₂). This does not seem to be an unrealistic possibility if one considers the relationship between these variables and gas exchange, and the effect insulin has on pulmonary gas transfer in patients with diabetes in addition to HF. The aims of this study were as follows:

1. to assess whether in cases with coexisting diseases, insulin ameliorates exercise performance and
2. to explore whether improvement in alveolar–capillary membrane conductance may have a role in these effects.
Abbreviations and Acronyms

\[ \text{DL}_{\text{CO}} = \text{lung diffusing capacity for carbon monoxide} \]
\[ D_M = \text{alveolar–capillary membrane diffusion capacity} \]
\[ \text{HF} = \text{heart failure} \]
\[ \text{peak VO}_2 = \text{oxygen consumption at peak exercise} \]
\[ \text{VA} = \text{alveolar volume} \]
\[ \text{VC} = \text{pulmonary capillary blood volume} \]
\[ \text{VCO}_2 = \text{available for gas exchange} \]
\[ \text{VE/VCO}_2 \text{ slope} = \text{slope of the increase in ventilation} \]
\[ \text{VO}_2 = \text{oxygen uptake} \]
\[ \text{VO}_2 \text{ AT} = \text{oxygen consumption at the anaerobic threshold} \]
\[ \Delta \text{VO}_2/\Delta \text{WR} = \text{rate of oxygen consumption increase per work rate} \]

METHODS

Study population. This study includes 18 patients who were referred for evaluation of chronic HF. All gave written consent to the procedures, and the research was approved by the ethical review committee of the hospital. All had type 2 diabetes mellitus and none had participated in previous studies in our laboratory. Carboxyhemoglobin concentration was <2%, a value compatible with that of non-smoking urban dwellers. Glycosylated hemoglobin levels averaged 6.2 ± 0.3% on therapy (the normal range in our laboratory is 4% to 5.5%). Hyperglycemia was controlled by diet alone (n = 2), or plus sulfonylurea (n = 9) or metformin (n = 7). These were consecutive patients who were enrolled if they had chronic stable New York Heart Association functional class II to III HF from previous myocardial infarction (n = 11) or idiopathic cardiomyopathy (n = 7) (cardiac enlargement without a specific cause for left ventricular impairment); if ejection fraction was <35%; and if they were able to complete a maximal cardiopulmonary exercise test. Pulmonary function was not a selection measure. Patients were excluded if they had hypertension, pulmonary disease, or had smoked >10 cigarettes per day during one of the past five years (all had abstained from tobacco products for at least nine months before enrollment, and four patients had never smoked); if exercise was limited by symptoms other than dyspnea or fatigue and they developed electrocardiographic changes of myocardial ischemia on effort; if they had clinically evident distal symmetrical neuropathy, autonomic insufficiency, or renal impairment, all of which can alter exercise performance (9). Patients who received beta-adrenergic blocking agents or who, at Doppler velocimetry, presented with mitral regurgitation exceeding grade 2 on a scale of 0 to 5 also were not included. The antifailure treatments prescribed by the referring physicians included digoxin, loop diuretics, and angiotensin-converting enzyme inhibitors in all, nitrates in two, and aspirin in five.

Pulmonary function. Diffusion of carbon monoxide (\( \text{DL}_{\text{CO}} \)) was assessed with Sensor Medics 2200 Pulmonary Function Test System (Anaheim, California). The measurement was determined twice with a standard, single-breath technique. Reference equations were used when values were expressed as percentage of normal predicted (14). The single-breath alveolar volume (VA) was derived by methane dilution. The subdivisions of \( \text{DL}_{\text{CO}} \), i.e., the alveolar–capillary membrane diffusion capacity (\( D_M \)) and the capillary pulmonary blood volume available for gas exchange (\( \text{VC} \)), were determined, according to the classic Roughton and Forster method (15), as previously reported (16). Lung diffusing capacity for carbon monoxide and its subcomponents were expressed in absolute values, as well as per unit of VA (\( \text{DL}_{\text{CO}}/\text{VA} \), \( D_M/\text{VA} \), \( \text{VC}/\text{VA} \)). The proportion of total pulmonary diffusive resistance ascribable to the alveolar–capillary interface was calculated (\( \text{DL}_{\text{CO}}/D_M \)).

Exercise. Cycle ergometry exercise was performed in an upright position, using an individualized ramp protocol according to the preliminary assessment of the patient’s functional capacity, to ensure a test duration of ~10 min and to avoid premature fatigue. Breath-by-breath gas exchange analysis was performed at rest and throughout exercise using a Sensor Medics Vmax 29C system (Yorba Linda, California). Respiratory gas was sampled continuously from a mouthpiece, and minute ventilation (VE), \( \text{VO}_2 \), carbon dioxide output (\( \text{VCO}_2 \)), and respiratory exchange ratio (RER) were calculated. The V-slope analysis was used to calculate the anaerobic threshold (AT). Ventilatory efficiency was assessed by calculating the slope of the increase in ventilation with respect to \( \text{CO}_2 \) production (VE/\( \text{VCO}_2 \) slope). Oxygen consumption at the AT, and the rate at which \( \text{VO}_2 \) increased per work rate (\( \Delta \text{VO}_2/\Delta \text{WR} \)), as an indicator of aerobic efficiency, were also measured. The rate at which \( \text{VO}_2 \) increased per work rate was calculated for the progressively increasing exercise period beginning 1 min after WR started to increase. The delay of 1 min after the start of increase in WR was used to take into account the time constant for \( \text{VO}_2 \) to respond to the increasing WR (around 35 s for normal subjects) (17). Peak \( \text{VO}_2 \) was determined by the highest \( \text{VO}_2 \) achieved during exercise. Age-, gender-, and weight-adjusted predicted \( \text{VO}_2 \) values were also determined. The maximal \( \text{O}_2 \) pulse was measured by dividing the highest \( \text{VO}_2 \) by the maximal heart rate.

Echocardiography. Two-dimensional and Doppler echocardiography were performed by standard methods. Pulmonary artery systolic pressure, left ventricular end-systolic and end-diastolic chamber dimensions and left ventricular volume, by the area–length method (to measure ejection fraction), were quantitated by standard techniques. Stroke volume was calculated as the velocity time integral of the systolic velocity spectrum in the outflow tract multiplied by the subaortic area of the outflow tract.

Protocol. All patients were admitted to the hospital, were maintained on their current drug treatment, and were fed a diet containing 160 g carbohydrate/day. Routine laboratory
work and cardiac evaluation were performed on the day of admission. On the second day, subjects were familiarized with exercise testing and performed a graded maximal exercise test to determine peak VO₂. On the third day, they underwent an evaluation of pulmonary function including exchange capacity, pulmonary artery systolic pressure, ejection fraction and cardiac output, as well as an individualized exercise ramp test; these measurements were taken as the reference baseline parameters. On the following day, infusion studies were performed after a 12-h overnight fast and withdrawal of the morning oral hypoglycemic drugs, in a sitting position, in a quiet room. A catheter needle was inserted into an antecubital vein of each arm for infusions and blood drawing, respectively. After 30 min rest, 50 ml normal saline were infused intravenously, at a rate of 1.0 ml/min, that either contained or did not contain 10 IU of regular insulin (Humulin; Eli Lilly and Co., Indianapolis, Indiana). Glycemia was determined before infusion, at 10-min intervals during infusion, and 60 min after completion of the same. Blood glucose was kept at the baseline level during the experiment by administering, when necessary, intravenous 20% dextrose solution according to glycemia; the supplemented volume ranged between 20 and 80 ml. Serum potassium levels remained above 3.8 mEq/l in each patient during all phases of the study.

Those in charge for exercise and those in charge for infusions were not admitted at the same time to the room where experiments were performed and were not allowed to communicate with each other. By this method the main outcome variables of the study were investigated in a blind fashion.

The short-term effects of insulin were investigated in all participants by re-evaluating lung and cardiac function at rest and exercise testing in the 60 min after infusion. On the following morning the same procedures were repeated while patients were switched to insulin or to inactive solution according to random design. To determine the duration of the insulin effects, all measurements were repeated after a two-day washout period and were taken as the reference baseline parameters for the second part of the study, in which insulin and saline were given again according to the protocol already described, the only difference being a 6-h interval before the post-infusion evaluations.

Statistical analysis. Values are expressed as mean ± SD. Multiple comparison ANOVA test was used to compare the responses to saline and to insulin infusions. The two sets of baseline reference measurements performed in the two parts of the study were analyzed using the paired samples Student’s t test.

The relationship between resting lung function tests and exercise parameters was assessed using the Pearson coefficient of correlation. A p value of < 0.05 was considered to be statistically significant. Statistical analyses were performed by means of Stata 7.0 package (Stata Corp., College Station, Texas).

Table 1. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>18</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>12/6</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>60.7 ± 6.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.9 ± 7.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>Etiology of HF, IHD/DCM</td>
<td>10/6</td>
</tr>
<tr>
<td>Digoxin, mg/day</td>
<td>0.25 ± 0.02</td>
</tr>
<tr>
<td>Furosemide, mg/day</td>
<td>73 ± 7.1</td>
</tr>
<tr>
<td>Mitral regurgitation, subjective scale (0–5)</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Vital capacity, % predicted</td>
<td>71.7 ± 12</td>
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<tr>
<td>Forced expiratory volume in 1 s, % predicted</td>
<td>82.6 ± 11</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>135 ± 14</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>222 ± 18</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>199 ± 13</td>
</tr>
<tr>
<td>Glycohemoglobin, %</td>
<td>6.2 ± 0.3</td>
</tr>
<tr>
<td>Duration of diabetes, yrs</td>
<td>9.2 ± 3.2</td>
</tr>
</tbody>
</table>

DCM = dilated cardiomyopathy; HF = heart failure; IHD = ischemic heart disease.

RESULTS

Table 1 and Table 2 show that in the baseline fasting glycemia and glycohemoglobin were moderately elevated, ejection fraction and cardiac index were depressed, systolic pulmonary pressure was raised, forced expiratory volume in 1 s and vital capacity were not consistent with airway obstruction, DLCO and DLCO/VA were reduced to 69.2 ± 5.8% and to 63.8 ± 10.9%, respectively, of predicted normal values (14) (below levels reported in the literature for HF alone) (18). The proportion of diffusive resistance ascribable to alveolar–capillary interface averaged 74.6 ± 7.4%. Peak VO₂ was compromised, and the VE/VCO₂ slope, in all patients but one, exceeded the value of 30, which is the upper normal limit (19). The ΔVO₂/ΔWR, which reflects the oxygen utilized per unit increase in work rate and is an index of aerobic efficiency, was below the lower normal limit of 8.6 (20) and averaged 7.8 ± 2.1 ml/W⁻¹min⁻¹.

At measurements accomplished in the 60 min after insulin infusion (Table 2) compared with those taken at baseline, systemic hemodynamics were steady, pulmonary systolic pressure was reduced. There was also a significant increase in carbon monoxide diffusion (DLCO, +12.5%) and its membrane component (DM, +21.6%). These changes, when expressed per unit of VA, were: DLCO/VA, +18.9%; DM/VA, +26.5%. Insulin also reduced the pulmonary capillary blood volume (VC, −16.3%) and (DLCO/DM, −9%). The individual values reported in Figure 1 show that in the great majority of patients there was an improvement of DLCO, DM, peak VO₂, and a decrease of VE/VCO₂ slope. Compared with baseline reference measurements, insulin augmented peak VO₂ by 2.2 ml/kg⁻¹min⁻¹ (+13.5%) and reduced VE/VCO₂ slope by 18%. There was also an increase in time to anaerobic threshold (+29.4%), O₂ pulse (+12.3%), and ΔVO₂/ΔWR (+21.2%). Saline alone, compared with baseline measurements, did not have any effect on the pulmonary gas exchange and exercise capacity.

Variations in peak VO₂ and VE/VCO₂ slope from baseline with insulin correlated significantly with those in...
DLCO (Fig. 2, r = 0.67 p = 0.002, and r = −0.73, p < 0.001, respectively). We did not find a correlation of age, time from diabetes diagnosis, glycohemoglobin, and baseline fasting blood sugar with DLCO or DM.

All changes were not present 24 h later at measurements performed in patients who were given saline alone as second test drug. On the contrary, in the second part of the study, measurements performed at 6 h after infusion showed that the improvement from baseline (reference values were not significantly different from those in the first part of the study) in DLCO, DM, peak VO2, VE/VCO2 slope, and ∆VO2/∆WR was persistent and statistically significant (Table 3).

**DISCUSSION**

The main information provided by this study is that in patients with coexistence of type 2 diabetes and HF, insulin was associated with amelioration in exercise ventilatory efficiency and VO2. Insulin also produced an improvement in the alveolar–capillary gas conductance that was significantly related with the decreased VE/VCO2 slope and the increased peak VO2. These effects were not due to variations in glycerina.

**Changes in DLCO versus changes in VE/VCO2 slope.** Elevation of the hydrostatic forces and upregulation of sodium transport across the capillary endothelium by HF (16,21), and disturbances in microvascular permeability by diabetes (8,22), may concur to facilitate alveolar interstitial fluid accumulation and impedance to gas exchange. Insulin has the potential to reduce interstitial fluid accumulation and shorten the gas diffusion path in patients with diabetes or comorbidity, through an increase in inotropy (23) and a decrease of impedance to left ventricular ejection (23) (resulting in a reduction of the pulmonary hydrostatic forces), and by an enhancement of the defective release in diabetes of endothelium-derived nitric oxide and vasodilatating prostaglandins (4,24–26). These substances are involved in the modulation of the pulmonary vascular tone and permeability and can reduce the tissue component of resistance to the oxygen transfer from the alveolus to its uptake by hemoglobin. How much of the benefit on gas exchange is due to a pulmonary vasodilating effect of insulin, which decreases pulmonary artery pressure, cannot be estimated. Previous observations, however, do not support a major role for changes in pulmonary hemodynamics. In fact, insulin is
not significantly effective on the impedance to gas transfer in HF patients without diabetes (13); hydralazine and isosorbide dinitrate, which are quite effective in reducing pulmonary artery pressure and arteriolar resistance in HF patients, fail to improve DLCO (27). The possibilities should also be considered that saline, the vehicle used for insulin infusion,
may have depressed the lung diffusing capacity in HF patients (28), or that aspirin counteracted the facilitating effect that angiotensin-converted enzyme inhibitors exert on alveolar–capillary membrane conductance (27). These effects, however, would tend, if anything, to attenuate the response to insulin; therefore, they do not detract from our results.

The origin of a steep slope of ventilation to CO₂ production on exercise may be multifactorial: increase of the ventilation required to overcome a large dead space, augmented central drive to ventilation originating from J-receptor activation in consequence of the distended interstitial space, bicarbonate buffering of accumulating lactic acid, reduced perfusion of ventilating lung, abnormal central or reflex chemosensitivity, overactive ergoreceptors, abnormal autonomic and baroreceptor control of the circulation (29,30). This study does not define which factor may be the target of the joint influence of diabetes and HF and whether insulin exerts a protective activity. However, the amelioration in alveolar–capillary conductance, as possibly mediated by reduction of lung interstitial space overdistention, and its correlation with the improvement in VE/VCO₂ slope are indicative of an involvement of the membrane effects of insulin in the ameliorated ventilatory efficiency. Likewise, the increase in time to AT (delayed reliance on anaerobic pathways for energy production) and in ∆VO₂/∆WR (potentiated aerobic efficiency), are consistent with an interference of insulin with several mechanisms underlying the enhancement of VE/VCO₂ slope in patients with comorbidity.

**Changes in DLCO versus changes in peak VO₂.** Improvement in exercising skeletal muscle perfusion (11,23) and glucose uptake (given the marked change in aerobic efficiency), and in cardiac output response to exercise (achievement of a higher O₂ pulse), may well explain the benefits of insulin on VO₂. Insulin has a physiological role to vasodilate skeletal muscle vasculature, and this action is impaired in states of insulin resistance, such as type 2 diabetes and chronic HF (23). The observed increase in ∆VO₂/∆WR is consistent with an improvement in exercising muscle perfusion and/or an increase in cardiac output (increase in O₂ pulse). Using a similar protocol, in a comparable group of HF patients without diabetes, Parsonage et al. (11) have seen a beneficial central (increase in cardiac output) and peripheral (augmented forearm blood flow) effect of insulin. The extent of skeletal muscle perfusion can be an important determinant of insulin-mediated glucose uptake (31). In our population, baseline peak RER averaged 1.02 and increased to 1.07 and 1.04, 60 min and 6 h after insulin, respectively. This is in favor of increased cellular glucose availability and improved substrate utilization.

Although the correlation between changes in DLCO and those in peak VO₂ may simply reflect association, a few compelling comments are in order. In HF, exercise raises the capillary pulmonary pressure and the fluid–flux transition (factors that underlie (7) alveolar–capillary membrane stress); the physiological increase in gas exchange during exercise is restrained at the level of the membrane (impeded increase in conductance because of excessive fluid filtration to the alveolar interstitium), and capillary recruitment for gas exchange is inadequate. Coexistence of diabetic disturbances in the microvessel permeability might enhance the excessive fluid passage in the interstitial space, which restrains gas conductance, and makes the capillary recruitment during exercise even more inadequate. In this setting, hyperventilation might help maintain oxygen alveolar tension at normal levels, but could precipitate premature

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**Table 3. Circulatory and Respiratory Values at Rest and Exercise Parameters in the Baseline and 6 h After Regular Insulin (10 IU) or Saline Infusions**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Insulin</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose, mg/dl</td>
<td>146 ± 11</td>
<td>141 ± 8</td>
<td>142 ± 10</td>
</tr>
<tr>
<td>Cardiac index, l/min/m²</td>
<td>2.41 ± 1.9</td>
<td>2.59 ± 2.0</td>
<td>2.52 ± 1.9</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>27.9 ± 0.6</td>
<td>27.1 ± 0.5</td>
<td>28.3 ± 0.7</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>33.3 ± 4.1</td>
<td>26.8 ± 3.2†‡</td>
<td>35.1 ± 4.5</td>
</tr>
<tr>
<td>DLCO, ml/min/mm Hg⁻¹</td>
<td>17.7 ± 3.2</td>
<td>20.9 ± 3.3†‡</td>
<td>18.1 ± 4.1</td>
</tr>
<tr>
<td>VO₂, ml/kg/min⁻¹</td>
<td>24.5 ± 6.4</td>
<td>29.2 ± 4.6§</td>
<td>24.1 ± 5.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>131 ± 11</td>
<td>130 ± 11</td>
<td>130 ± 10</td>
</tr>
<tr>
<td>Peak systolic blood pressure, mm Hg</td>
<td>158 ± 20</td>
<td>159 ± 18</td>
<td>160 ± 20</td>
</tr>
<tr>
<td>Peak workload, W</td>
<td>95 ± 25</td>
<td>104 ± 24†‡</td>
<td>96 ± 30</td>
</tr>
<tr>
<td>Peak VO₂, ml/kg/min⁻¹</td>
<td>15.7 ± 1.9</td>
<td>18.3 ± 2.3†‡</td>
<td>15.3 ± 3.2</td>
</tr>
<tr>
<td>Peak VO₂, % predicted</td>
<td>76.6 ± 3.8</td>
<td>85.8 ± 4.2†‡</td>
<td>77.2 ± 3.1</td>
</tr>
<tr>
<td>Workload at AT, W</td>
<td>58 ± 25</td>
<td>69 ± 25†‡</td>
<td>60 ± 25</td>
</tr>
<tr>
<td>AT, min</td>
<td>3.1 ± 0.6</td>
<td>3.6 ± 0.8</td>
<td>3.2 ± 0.5</td>
</tr>
<tr>
<td>VO₂ AT, ml/kg/min⁻¹</td>
<td>11.2 ± 2.8</td>
<td>12.8 ± 3.4</td>
<td>11.5 ± 3.3</td>
</tr>
<tr>
<td>O₂ pulse, ml/beat</td>
<td>9.2 ± 1.8</td>
<td>9.8 ± 2.3</td>
<td>9.0 ± 2.4</td>
</tr>
<tr>
<td>Peak VE, l/min</td>
<td>61 ± 20</td>
<td>62 ± 22</td>
<td>60 ± 24</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.02 ± 0.3</td>
<td>1.04 ± 0.3</td>
<td>1.01 ± 0.3</td>
</tr>
<tr>
<td>VE/VCO₂ slope</td>
<td>40.3 ± 4.3</td>
<td>34.1 ± 4.1§</td>
<td>39.2 ± 3.8</td>
</tr>
<tr>
<td>∆VO₂/∆WR, ml/kg-min⁻¹</td>
<td>7.4 ± 2.6</td>
<td>9.2 ± 2.2†‡</td>
<td>7.0 ± 1.8</td>
</tr>
</tbody>
</table>

* p < 0.01 vs baseline; †p < 0.05 vs. baseline; ‡p < 0.05 vs. saline; §p < 0.01 vs. saline; †means of 14 patients.

Abbreviations as in Table 2.
exhaustion of the ventilation reserve (32) and early interruption of exercise. Consistent with this interpretation are the correlations reported in HF patients between peak VO₂ and lung diffusion (31,32), as well as the acute decrease of peak VO₂ and increase of VE/VCO₂ slope after an acute depression of D₅₃ (33).

These considerations substantiate the possibility that a compromised gas exchange efficiency participates in depressing both peak VO₂ and ventilatory efficiency in diabetes–HF comorbidity, and that it represents a background for the benefits of insulin on these variables. It is significant that the two patients in whom peak VO₂ reduced with insulin also showed worsening of ventilatory efficiency and membrane conductance (Fig. 1). Findings at 6 h suggest that the insulin-mediated changes are prolonged. This is a significant point in relation to a hypothetical therapeutic applicability.

Study limitations. The existence of a dose-related effect has not been defined. It is also unknown whether insulin resistance in type 2 diabetes (1) and HF (11) was at work in patients with comorbidity, and influenced the responses to the exogenous infusion of the hormone, and whether ACE inhibition, which exerts several protective influences in diabetes (3), can add to insulin’s effects.

Conclusions. Insulin in type 2 diabetes–HF comorbidity improves exercise performance. Several factors are likely involved in these effects; a facilitation of gas conductance at the lung level seems to play a significant role.

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