Peripheral muscle ergoreceptors and ventilatory response during exercise recovery in heart failure

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Francis, Noelle, Alain Cohen-Solal, and Damien Logeart. Peripheral muscle ergoreceptors and ventilatory response during exercise recovery in heart failure. Am. J. Physiol. 276 (Heart Circ. Physiol. 45): H913–H917, 1999.—Recent studies have suggested that the increased ventilatory response during exercise in patients with chronic heart failure was related to the activation of muscle metaboreceptors. To address this issue, 23 patients with heart failure and 7 normal subjects performed arm and leg bicycle exercises with and without cuff inflation around the arms or the thighs during recovery. Obstruction slightly reduced ventilation and gas exchange variables at recovery but did not change the kinetics of recovery of these parameters compared with nonobstructed recovery; half-time of ventilation recovery was 175 ± 54 to 176 ± 40 s in patients and 155 ± 66 to 127 ± 13 s in controls (P < 0.05, patients vs. controls, not significant within each group from baseline to obstructed recovery). We conclude that muscle metaboreceptor activation does not seem to play a role in the exertion hyperventilation of patients with heart failure.

METHODS

We used two protocols to assess the ergoreceptor response of the legs and arms.

Protocol 1. Protocol 1 was designed to assess the ergoreceptor responses of the lower limbs.

All exercise tests were performed in the morning after a light breakfast. We used an upright graded bicycle exercise with workload increments of 10 W/min for the patients and 20 W/min for the control group, after a similar initial workload of 20 W. Patients and control subjects were regularly encouraged to exercise until exhaustion. The bicycle was an Ergoline 900 ergometer, the calibration of which was regularly checked; subjects pedaled at a constant rate of 40–50 rpm. At maximal exercise the load was removed and the subjects were asked to stop pedaling.

Respiratory gas analysis was carried out with a CPX-D Medical Graphics system (St. Paul, MN). Calibration of the system was performed with standard gas of known concentration before each test. Subjects were asked to remain still for 3 min before exercising to stabilize resting gas measurements. A standard 12-lead electrocardiogram was continuously recorded, allowing determination of heart rate each minute. Blood pressure was measured by a sphygmomanometer every 2 min. O₂ consumption (V˙O₂), CO₂ production (V˙CO₂), minute ventilation (V˙E), breathing rate, respiratory exchange ratio, ventilatory equivalents for V˙O₂ (Ve/V˙O₂) and V˙CO₂ (Ve/V˙CO₂), and end-tidal P O₂ (PETO₂) and P CO₂ (PETCO₂) were measured on a breath-by-breath basis. The results were averaged using a moving-average filter every seven breaths, with the highest and lowest values excluded at each breath to reduce the breath-by-breath noise. They were thereafter averaged every 15 s and printed. Peak V˙O₂ was defined as the highest V˙O₂ obtained at the end of the test; it was expressed in milliliters per minute and in milliliters per minute per kilogram. Indexed peak V˙O₂ (percent) was calculated as peak V˙O₂ divided by maximal predicted V˙O₂ with use of the values reported by Wasserman et al. (34). The ventilatory threshold was determined by classical methods (8, 35).
Ventilation response was assessed during recovery by means of the half-time of recovery ($t_{1/2}$) of ventilatory variables with use of a previously reported method (9). The kinetics of recovery of gas exchange and ventilatory variables ($V_O_2$, $V_CO_2$, $V_E$) fit a single-exponential curve (3, 12, 14, 16). The single-exponential regression between $V_O_2$, $V_CO_2$, and $V_E$ and time during the first 4 min of recovery was described by the slope ($k$) and the relationship as follows: $y(t) = Ae^{-kt} + C$, where $k$ (the rate constant) is the slope of the curve, $A$ is a parameter, and $C$ is the asymptotic baseline value. We then derived $\tau$, the constant of time, defined as $\tau = 1/k$ and $t_{1/2}(\text{exp}) = 0.693\tau$. We also characterized recovery kinetics by simply measuring $t_{1/2}$, i.e., the time required for a 50% fall in the peak value, as previously reported (9). The coefficients of variation of these variables were recently found to be 6 and 12% (9). Results obtained by these two methods were here again highly correlated; therefore, only those obtained by the exponential method are reported here.

On the next day, patients and subjects underwent the same test at the same time of day. A large cuff was positioned around the lower part of the thighs before the test and inflated for 30 s to evaluate the tolerance to inflation. All patients were able to endure the occlusion. After 10 min, subjects underwent the graded exercise test. At peak exercise, the cuffs were rapidly inflated at suprasystolic pressure (i.e., the systolic pressure measured at peak exercise during the preliminary test). Subjects were asked to have their legs extended during recovery to ensure perfect occlusion of circulation. Circulatory occlusion was maintained during 3 min of recovery, then released.

Protocol 2. Protocol 2 was performed to assess the role of the upper limb muscle ergoreceptors.

Exercise was performed with the arms by using a specially designed cycle ergometer. The patient was seated, with the chest at the level of the ergometer. Work rate was increased by 5 W/min after an initial work rate of 10 W in patients and by 10 W/min after an initial work rate of 20 W in normal subjects. All subjects performed exercise to a maximum effort while gas exchange was measured on-line.

Circulatory occlusion was made during a second test, at peak exercise, with two smaller cuffs inflated around the upper part of the arm. However, inflation pressure was 40–50 mmHg only, because no subject could tolerate an inflation at suprasystolic pressure. Thus this level of inflation was considered sufficient to induce venous, but not arterial, occlusion. The kinetics of ventilation were assessed as described for protocol 1.

Subjects. Twenty-three men with mild to moderate CHF (57 ± 6 yr of age) and 7 normal men (50 ± 2 yr of age) participated in the study. Patients with CHF were categorized as New York Heart Association functional class II (n = 13) or III (n = 10). All had performed at least one preliminary exercise test, which was terminated because of fatigue and/or dyspnea. The causes of heart failure were ischemic (n = 11) or idiopathic (n = 12) cardiopathies. Mean left ventricular ejection fraction was 27 ± 13%. None of the patients had valve disease or respiratory insufficiency. All patients were receiving diuretics and angiotensin-converting enzyme inhibitors, and one-half of them were receiving digitalis; none was receiving a β-blocker. Ongoing treatments were not stopped before the exercise test. None of the control subjects had clinical signs of heart failure or echographic evidence of left ventricular dysfunction or pulmonary disease.

Nineteen patients performed protocol 1, and 12 performed protocol 2. Normal subjects performed protocols 1 and 2.

All the subjects gave their informed consent, and the study protocol was approved by the local ethics committee.
subjects (15, 31), suggests that $\dot{V}E$ still responded in proportion to the $\dot{V}CO_2$ from the exercising muscles. $\dot{V}E/\dot{V}CO_2$ was observed during the obstructed recovery, despite changes in $\dot{V}E$, as in previous studies in normal studies. The fact that no significant change in $PETCO_2$ or included from circulation was less than in previous parts of the thighs. Therefore, the muscle mass also be due to the fact that we occluded only the lower decreased (Fig. 1) compared with the control test may decreased after cuff inflation, which was in opposition to fact that blood pressure during recovery was greater slowly with than without cuff inflation; however, the response, inasmuch as heart rate did not decrease more from circulation was less than in previous studies. The fact that ventilation levels were always slightly lower with cuff inflation, but this trend was not significant. Half-time of recovery of ventilation was not significantly different between tests. Values are means ± SD.

Our findings do not necessarily contradict the previous studies (11, 15, 18, 31) because of differences in protocol and in the way in which the recovery rate of ventilation was assessed. The absolute decrease in ventilatory level was far greater in the study of Haouzi et al. (15), who used supra-anaerobic constant work rate exercise, than in that of Innes et al. (18), who used a moderate level of exercise. The fact that ventilation levels after circulatory occlusion were only moderately decreased (Fig. 1) compared with the control test may also be due to the fact that we occluded only the lower parts of the thighs. Therefore, the muscle mass excluded from circulation was less than in previous studies. The fact that no significant change in $PETCO_2$ or $\dot{V}E/\dot{V}CO_2$ was observed during the obstructed recovery, despite changes in $\dot{V}E$, as in previous studies in normal subjects (15, 31), suggests that $\dot{V}E$ still responded in proportion to the $\dot{V}CO_2$ from the exercising muscles.

Recently, Piepoli and co-workers (28, 29) suggested that abnormalities of muscle metabolism play a major role in the exertional dyspnea of patients with CHF, launching the attractive “muscle hypothesis” of exertional dyspnea (6, 7). These authors found that circulatory occlusion virtually totally impeded the decrease of exertional hyperventilation after peak exercise, until cuffs were deflated. They concluded that circulatory occlusion, by trapping locally the products of metabolism, led to an increased stimulation of muscle ergoreceptors. This result was also found in normal subjects (28), in contrast to previous studies (15, 18). It is difficult to reconcile our findings with their results. We used maximal graded exercise, whereas they used handgrip. The level of exercise was also much lower than in their study (peak exercise $\dot{V}O_2$ was <500 ml/min) than in ours, which was done maximally, because we expected the metabolites trapped within the muscles to be at the highest possible concentration. Their exercise tests were performed with the arms and with cuffs inflated at suprasystolic pressure. We used leg and arm exercise, but we were unable to achieve circulatory occlusion of the arms at suprasystolic pressure after exercise, because this maneuver was extremely painful, and neither patients nor normal subjects tolerated it for >30 s. However, 40–50 mmHg seems sufficient to block venous return in the arm and to trap metabolites within the muscles, which was the aim of the protocol. Piepoli et al. (28, 29) stated that stimulation of nociceptive fibers could not explain the persistent ventilatory response, inasmuch as heart rate did not decrease more slowly with than without cuff inflation; however, the fact that blood pressure during recovery was greater after cuff inflation may suggest that pain indeed elicited a nociceptive response that could by itself explain hyperventilation. $\dot{V}O_2$ and mainly $\dot{V}CO_2$ were also increased after cuff inflation, which was in opposition to what others have found; finally, this increased $\dot{V}CO_2$ response at recovery could not be reproduced in the second study performed in CHF patients. The relative level of persistent hyperventilation in normal subjects and in CHF patients was compared and found to be greater in CHF patients.

Despite the fact that the rate of decrease of ventilation after exercise was not affected by cuff inflation, ventilation tended to be lower than without cuff inflation at each measurement during recovery. These results are thus in accordance with those reported by

### Table 2. Peak $\dot{V}O_2$ and half-time of $\dot{V}E$, $\dot{V}CO_2$, and $\dot{V}O_2$ recoveries with and without cuff inflation after arm exercise in CHF patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>CHF Patients</th>
<th>Control Subjects</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Cuff inflated</td>
</tr>
<tr>
<td>Peak $\dot{V}O_2$, ml·min⁻¹·kg⁻¹</td>
<td>17 ± 2*</td>
<td>17 ± 2*</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>124 ± 18*</td>
<td>128 ± 29*</td>
</tr>
<tr>
<td>$\dot{V}O_2$</td>
<td>134 ± 27*</td>
<td>143 ± 37*</td>
</tr>
<tr>
<td>$\dot{V}CO_2$</td>
<td>175 ± 54*</td>
<td>176 ± 40*</td>
</tr>
<tr>
<td>$\dot{V}E$</td>
<td>66 ± 20*</td>
<td>67 ± 20*</td>
</tr>
</tbody>
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Values are means ± SD. All variables differed significantly in patients vs. normal subjects (*P < 0.05), but there was no significant difference with and without cuff inflation in either group.

### Fig. 1. Recovery of ventilation after maximal exercise in patients with heart failure with and without cuff inflation. Overall, ventilation levels were always slightly lower with cuff inflation, but this trend was not significant. Half-time of recovery of ventilation was not significantly different between tests. Values are means ± SD.

### Fig. 2. Changes in end-tidal $PCO_2$ ($PETCO_2$) during recovery with and without cuff inflation. There was no significant difference in responses.
Rowell et al. (31), Innes et al. (18), and Haouzi et al. (15). The mechanism of reduction in Ve during circulatory occlusion is still debated. It is classically attributed to reduction of flow of known or unknown metabolites to the arterial or central chemoreceptors (17). H+ and K+ have been incriminated, but a discrepancy between the rate of lactate removal and ventilatory decline has been usually found (27) and other mechanisms probably also operate. Recently, it was demonstrated that chemoreceptor sensitivity was increased in CHF patients (5), which may explain the greater ventilatory response of CHF patients for a given amount of CO2. NMR spectroscopy studies demonstrated that the difference in protocol between normal subjects and CHF patients may have confounded our results. It is also unlikely that the difference in protocol between normal subjects and CHF patients had been regularly exercised on a bicycle for other studies or in the setting of the regular evaluation of their disease. A familiarization effect was thus unlikely to have occurred. It is also unlikely that the difference in protocol between normal subjects and CHF patients may have confounded our results. Our study was not aimed at elucidating the various mechanisms responsible for the exertional dyspnea in CHF patients. Our results favor the hypothesis suggested by Rowell et al. (31) and Wasserman et al. (34, 35) of a predominant role of hyperventilation linked to CO2 production by a still unknown mechanism. The decrease in ventilation at a similar level of exercise found after training in CHF patients and attributed to improvement in muscle metabolism may be explained by reduced stimulation of aortic and carotid chemoreceptors secondary to reduced central delivery of CO2.

Conclusion. Cuff inflation of the legs or the arms at peak exercise does not retard the decline of ventilation in CHF patients or in normal subjects. This argues against a significant role of muscle chemoreceptors in genesis of the exercise hyperventilation of patients with CHF.

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