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.

PATIENTS WITH CHRONIC HEART failure (CHF) have an excessive ventilation during exercise (36) and recovery (9). Such exertional hyperventilation does not seem to be related to increased pulmonary capillary pressure (13). Increased pulmonary dead space (33), bronchial hyperreactivity (2), and heavy respiratory muscle work (22) have also been suggested as possible mechanisms. A classical view links the increased ventilatory response to exercise to stimulation of the carotid chemoreceptors by CO₂ produced by the muscles during exercise (31); it was recently suggested that muscle metaboreceptors may mediate the hyperventilation response during and after exercise in CHF (6, 28) and that the decreased ventilation brought about by training was due to their decreased stimulation (29). Ergoreceptors are receptors sensitive to physical stimuli, e.g., pressure and tension (“mechanoreceptors”), or to metabolic stimuli, e.g., H⁺, lactate, and K⁺ (“metaboreceptors”), that stimulate ventilation via excitation of myelinated type III and nonmyelinated type IV muscle fibers (26, 30).

We undertook this study to assess the role of ergoreceptor stimulation in exertional dyspnea of patients with CHF. If ergoreceptor stimulation plays a role in exercise hyperventilation, trapping the products of local metabolism within the muscle by cuff inflation should excite them. Inasmuch as CHF patients exhibit marked histological (23) and metabolic muscle abnormalities (21), greater decrease in intracellular pH (21) and increase in K⁺ (1) during exercise should excite metaboreceptors, whereas increased venous pressure and capillary filtration (19) should stimulate ergoreceptors. Thus the contribution of muscle ergoreceptors to hyperventilation should be greater in CHF patients than in normal subjects. Our hypothesis was that circulatory occlusion, maintaining metabolites within the muscle, would retard the normal decrease of ventilation after exercise in CHF patients. We sought also to determine whether a regional heterogeneity was present in the ergoreceptor response, inasmuch as it is now clearly demonstrated that muscle abnormalities exhibit regional differences, as recently demonstrated for muscle vascular reactivity (20), perhaps because of differential deconditioning (4).

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. Oxygen consumption (VO₂), CO₂ production (VCO₂), minute ventilation (VE), breathing rate, respiratory exchange ratio, ventilatory equivalents for VO₂ (VE/VO₂) and VCO₂ (VE/VCO₂), and end-tidal PO₂ (PetO₂) and PCO₂ (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 VO₂ was defined as the highest VO₂ obtained at the end of the test; it was expressed in milliliters per minute and in milliliters per minute per kilogram. Indexed peak VO₂ (percent) was calculated as peak VO₂ divided by maximal predicted VO₂ 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 ($V_{\text{O}2}$, $V_{\text{CO}2}$, $V_{\text{E}}$) fit a single-exponential curve (3, 12, 14, 16). The single-exponential regression between $V_{\text{O}2}$, $V_{\text{CO}2}$, and $V_{\text{E}}$ and time during the first 4 min of recovery was described by the slope ($k$) of 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 $t_{1/2}$, the constant of time, defined as $t_{1/2} = 1/k$ and $t_{1/2}(\text{exp}) = 0.693k$. 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.

Table 1. Peak $V_{\text{O}2}$ and half-time of $V_{\text{E}}$, $V_{\text{CO}2}$, and $V_{\text{O}2}$ recoveries after peak leg exercise with and without cuff inflation in CHF patients and control subjects

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<th>CHF Patients</th>
<th>Control Subjects</th>
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<td></td>
<td>Baseline</td>
<td>Cuff inflated</td>
</tr>
<tr>
<td>Peak $V_{\text{O}2}$, ml·min$^{-1}$·kg$^{-1}$</td>
<td>22 ± 2*</td>
<td>22 ± 4*</td>
</tr>
<tr>
<td>$t_{1/2}$, s</td>
<td>122 ± 17*</td>
<td>118 ± 29*</td>
</tr>
<tr>
<td>$V_{\text{O}2}$</td>
<td>136 ± 34*</td>
<td>129 ± 36*</td>
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<tr>
<td>$V_{\text{CO}2}$</td>
<td>147 ± 36*</td>
<td>137 ± 42*</td>
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Values are means ± SD. Comparison of $t_{1/2}$ values was carried out with paired or unpaired Student's t-test as appropriate. ANOVA for repeated measurements was used to compare change in $V_{\text{E}}$, $V_{\text{E}}/V_{\text{O}2}$, $V_{\text{E}}/V_{\text{CO}2}$, $P_{\text{ETO}2}$, and $P_{\text{ETCO}2}$ with and without cuff inflation at recovery. $P < 0.05$ was considered significant.

RESULTS

Protocol 1. Patients and subjects reached comparable work rates and peak $V_{\text{O}2}$ during the two tests (Table 1). Cuff inflation could be maintained during recovery in all subjects. The $t_{1/2}$ of ventilatory variables of the patients was within values previously reported (9, 10). $V_{\text{O}2}$, $V_{\text{CO}2}$, and $V_{\text{E}}$ recovery rates were lower in patients than in normal subjects ($P < 0.05$). Although values were slightly lower at each level during circulatory occlusion (Fig. 1), there was no significant difference in the $t_{1/2}$ of $V_{\text{E}}$, $V_{\text{O}2}$, or $V_{\text{CO}2}$ with and without cuff inflation in patients and in normal subjects. $V_{\text{E}}/V_{\text{O}2}$, $V_{\text{E}}/V_{\text{CO}2}$, $P_{\text{ETO}2}$, and $P_{\text{ETCO}2}$ courses were unaffected by cuff inflation (Fig. 2).

Protocol 2. Both tests were also well reproducible. Here again, no difference in the kinetics of recovery was observed in any variable with and without cuff inflation (Table 2).

DISCUSSION

The main finding of this study is that circulatory occlusion did not affect the ventilatory response in CHF patients more than in normal subjects after exercise, suggesting that a greater stimulatory response from the muscle ergoreceptors does not explain the exercise ventilation observed in CHF patients.

Circulatory occlusion produced by cuff inflation decreases ventilation at each level of exercise, as demonstrated previously (11, 15, 18, 31). These results have been interpreted as showing that trapping blood in the exercised legs during exercise recovery accelerates the ventilatory decline to resting levels. In these studies, however, the rate of ventilatory recovery was not directly calculated. Moreover, these studies were performed during constant submaximal work rate exercise, whereas our study used graded maximal exercise.
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 PETCO2 or excluded from circulation was less than in previous parts of the thighs. Therefore, the muscle mass ex-

also be due to the fact that we occluded only the lower levels after circulatory occlusion were only moderately

a moderate level of exercise. The fact that ventilation rate exercise, than in that of Innes et al. (18), who used supra-anaerobic constant work 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 maximal graded exercise, whereas they used handgrip. The level of exercise was also much lower in their study (peak exercise \( \dot{V}O_2 \) was \(<500 \text{ ml/min}\) 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 suprasystemic pressure. We used leg and arm exercise, but we were unable to achieve circulatory occlusion of the arms at suprasystemic pressure after exercise, because this maneuver was extremely pain-

ful, and neither patients nor normal subjects tolerated it for \( >30 \text{ s} \). 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 with than without cuff inflation, but this trend was not significant. Half-time of recovery of ventilation was not significantly different between tests. Values are means \( \pm \) 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 PETCO2 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 in their study (peak exercise \( \dot{V}O_2 \) was \(<500 \text{ ml/min}\) 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 suprasystemic pressure. We used leg and arm exercise, but we were unable to achieve circulatory occlusion of the arms at suprasystemic pressure after exercise, because this maneuver was extremely pain-

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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

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<td>Baseline</td>
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<tr>
<td>( \dot{V}O_2 ) ( \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} )</td>
<td>( 17 \pm 2^* )</td>
<td>( 17 \pm 2^* )</td>
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<tr>
<td>( V_{t,5} )</td>
<td>( 124 \pm 18^* )</td>
<td>( 128 \pm 29^* )</td>
</tr>
<tr>
<td>( V_{O_2} )</td>
<td>( 134 \pm 27^* )</td>
<td>( 143 \pm 37^* )</td>
</tr>
<tr>
<td>( V_{CO_2} )</td>
<td>( 175 \pm 54^* )</td>
<td>( 176 \pm 40^* )</td>
</tr>
<tr>
<td>( V_e )</td>
<td>( 29 \pm 11^* )</td>
<td>( 40 \pm 15^* )</td>
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Values are means \( \pm \) 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.

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

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 \( \pm \) SD.
Rowell et al. (31), Innes et al. (18), and Haouzi et al. (15). The mechanism of reduction in $V_e$ 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 CO$_2$. NMR spectroscopy studies demonstrated that the decrease in tissue pH is greater at peak exercise in CHF patients than in normal subjects, suggesting greater production of acid products (21, 24, 25). A recent work suggested that ergoreceptor stimulation, assessed by microneurographic response, is lower in CHF patients than in normal subjects (32). Therefore, a decreased sensitivity of the muscle receptor in CHF may explain the lower microneurographic response, despite increased production of metabolites within the muscles.

Subjects were studied according to a fixed sequence with a test with cuff occlusion always following the baseline test without cuff occlusion. It is, however, unlikely that this has biased the study, inasmuch as 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 CO$_2$ 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 CO$_2$.

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 ergoreceptors in genesis of the exercise hyperventilation of patients with CHF.

The authors acknowledge the remarks and comments of Karlman Wasserman and Philippe Haouzi.

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Received 11 August 1998; accepted in final form 10 November 1998.

REFERENCES


