

Hemodynamic, Ventilatory and Metabolic Effects of Light Isometric Exercise in Patients With Chronic Heart Failure

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Light isometric exercise, such as lifting or carrying loads that require 25% of a maximal voluntary contraction, is frequently reported to cause dyspnea in patients with heart failure. The pathophysiologic mechanisms responsible for the appearance of this symptom, however, are unknown. Accordingly, hemodynamic, metabolic and ventilatory responses to 6 min of light isometric forearm exercise were examined and compared in 20 patients with chronic heart failure and abnormal ejection fraction ($24 \pm 9\%$) and 17 normal individuals. In contrast to findings in normal volunteers, exercise cardiac index did not increase whereas exercising forearm and mixed venous lactate concentrations increased ($p < 0.05$) above levels at rest in patients with heart failure; at 90 s of recovery, blood lactate concentra-

tion remained elevated ($p < 0.05$). The venous lactate concentration of the nonexercising arm, unlike that of the exercising forearm, was not altered. Oxygen uptake, carbon dioxide production and minute ventilation increased similarly in patients and normal subjects during exercise, but only in patients did each increase further ($p < 0.05$) during recovery.

Thus, in patients with heart failure, light isometric forearm exercise represents an anaerobic contraction with lactate production. The subsequent increase in carbon dioxide production leads to a disproportionate increase in minute ventilation and oxygen uptake during recovery that may be perceived as breathlessness.

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Normal daily activities for patients with chronic heart failure include light isometric exercise, such as lifting and carrying loads that require 25% of a maximal voluntary contraction. Such tasks, however, are often reported to be associated with breathlessness. The pathophysiologic response that accounts for this effort intolerance is of clinical interest. In previous studies (1,2) of forearm handgrip exercise in patients with left ventricular dysfunction, a normal elevation in systemic arterial pressure and heart rate was observed. In the patients, however, unlike normal subjects, cardiac output and stroke-volume failed to increase even though left ventricular filling pressure increased substantially. Because these patients are unable to adequately increase systemic blood flow during isometric exercise (1,2) or isotonic exercise (3), we hypothesized that light isometric exercise would

lead to lactate production. As a result, ventilatory drive and minute ventilation would be increased by the enhanced carbon dioxide production that accompanies lactic acid buffering by bicarbonate. This concept is not dissimilar to that of the reduced lactate threshold to isotonic exercise previously observed in such patients (3). To test this hypothesis, we undertook this study to characterize, and to compare with findings in normal individuals, the metabolic, ventilatory and hemodynamic responses to light isometric forearm exercise in patients with chronic stable heart failure.

Methods

Study patients. The study group included 20 patients with clinically stable chronic heart failure (New York Heart Association classes II to IV). There were 17 men and 3 women ranging in age from 26 to 76 years (mean 58 ± 12). The cause of their heart failure was idiopathic dilated cardiomyopathy in 12 patients and ischemic heart disease with previous myocardial infarction in 8. None of the patients had a myocardial infarction or unstable angina within the 3 months preceding enrollment in the study. The radionuclide ejection fraction for the group was $24 \pm 9\%$.

Seventeen normal individuals (11 men), ranging in age

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from 23 to 48 years (mean 30 ± 10), were also studied as a control group. There was no history or clinical evidence of cardiac or noncardiac disease in these individuals. Informed consent to participate in this study was obtained from all patients and normal subjects.

Gas exchange monitoring. With the nose clamped and the subject breathing into a nonbreathing valve chamber, oxygen and carbon dioxide partial pressures of expired air were monitored on a breath by breath basis in 11 of the 20 patients and 10 of the 11 normal volunteers. An air flow sensing device was used to monitor tidal volume and respiratory rate. From these data, oxygen uptake, carbon dioxide production and minute ventilation were calculated with standard formulas (4).

Hemodynamic and metabolic monitoring. Hemodynamic and metabolic monitoring was performed in 7 of the 11 patients and 5 of the 10 normal individuals who had agreed to participate in other research protocols approved by the investigational review board of our hospital. These protocols required the placement of a triple lumen flotation catheter into the pulmonary artery and a cannula into a radial artery to assess the response of cardiac output, right and left ventricular filling pressures, mixed venous lactate concentration and arterial pressure. The present study was conducted before the initiation of these protocols. Baseline hemodynamic measurements were obtained ≥ 2 h after catheter insertion. Arterial and mixed venous blood were also sampled for oxygen saturation. Cardiac output was determined by the Fick principle with use of systemic arteriovenous oxygen difference and directly measured oxygen uptake (see later). Systemic oxygen extraction was calculated as the ratio of the arteriovenous oxygen difference to arterial oxygen content $\times 100$. Cardiac index and stroke index were calculated by standard methods.

In an additional nine patients and seven normal volunteers, a cannula was positioned in the basilic vein of the exercising forearm to sample venous blood for its oxygen saturation and lactate concentration before, during and after light isometric exercise. Four of the patients also had a cannula placed in the basilic vein of the nonexercising forearm for measurement of oxygen (O_2) saturation and lactate concentration during exercise.

Isometric exercise protocol. All medications were withheld for 18 h before the study. Before undertaking handgrip exercise, the patient was instructed in the use of a hand dynamometer and how to breathe normally without breath-holding or the Valsalva maneuver. Thereafter, with a calibrated hand dynamometer (Fitness Products), maximal voluntary contraction (in pounds) was obtained with the patient in the sitting position; this is the maximal load that can be attained. The average levels of maximal voluntary contraction were 84 ± 4 and 76 ± 4 lb (31.3 ± 1.5 and 28.3 ± 1.5 kg for the normal and heart failure groups, respectively). After 1 h of bed rest, light (25% maximal voluntary contraction)

isometric exercise was performed for 6 min. This level of exercise was maintained by visual feedback to the patient. The hemodynamic, ventilatory and metabolic responses were monitored during the 2 min before the contraction, during the 6 min of contraction and for the first 2 min of recovery.

The following data points during 6 min of exercise and for 2 min after exercise were selected for analysis. Beginning with the 6th min of exercise and the 1st min of recovery, when responses tended to be maximal, right atrial, pulmonary artery, pulmonary capillary wedge and systemic arterial pressures were recorded. Thereafter, blood samples for metabolic measurements were taken. Breath by breath measurements of oxygen uptake, carbon dioxide production and ventilation were averaged during the last 30 s of exercise and during the 30 s after the 1st min of recovery.

Statistical analysis. All data are presented as mean \pm SEM. Percent changes were computed for each variable from their level at rest to peak exercise and to 90 s of recovery. Data were analyzed with two-way analysis of variance for repeated measures. Specifically, one "group factor" with two levels (that is normal and heart failure) and one "within factor" with three levels (that is, baseline, exercise and recovery) were used. If the analysis of variance indicated a significant difference (significant F ratio) then pairwise comparisons were made to identify the exact nature of these differences. We limited the analysis to the following seven pairs: four within-group comparisons (normal baseline versus normal exercise, normal baseline versus normal recovery, heart failure baseline versus heart failure exercise and heart failure baseline versus heart failure recovery) and three between-group comparisons (normal baseline versus heart failure baseline, normal exercise versus heart failure exercise and normal recovery versus heart failure recovery). Statistical significance for the pairwise comparison was assessed using Bonferroni bounds to account for multiple simultaneous comparisons. The significance level was set at $p < 0.05$.

Results

Hemodynamic response. The peak hemodynamic response to light isometric handgrip exercise and its recovery is given in Table 1. Heart rate, which was significantly higher in patients at rest than in normal subjects, increased significantly by 12 and 10%, respectively, in both patients and normal subjects at peak exercise and returned to its level at rest within 90 s of recovery. Mean arterial pressure at rest was not different between groups; it increased ($p < 0.05$) in similar proportions at peak exercise and remained elevated above baseline during recovery.

Cardiac index at rest, not unexpectedly, was lower in patients than in normal subjects. During exercise, cardiac index increased by 58% in the control group, whereas it

Table 1. Hemodynamic Response to Peak Light Isometric Exercise and 90 s of Recovery in Seven Patients With Heart Failure and Five Normal Individuals

	At Rest		Exercise		Recovery	
	N	F	N	F	N	F
Heart rate (beats/min)	73 ± 4	91 ± 6†	80 ± 4*	99 ± 5†*	77 ± 4	96 ± 5†
Mean arterial pressure (mm Hg)	95 ± 4	94 ± 6	113 ± 6*	108 ± 6*	103 ± 5*	102 ± 6*
Cardiac index (liters/min per m ²)	2.9 ± 0.3	1.9 ± 0.3	4.4 ± 1.1†*	1.9 ± 0.2	3.1 ± 0.4	2.7 ± 0.2
Stroke index (ml/m ²)	39 ± 7	23 ± 4	50 ± 10	20 ± 3†	40 ± 5	28 ± 8
RA pressure (mm Hg)	3 ± 1	4 ± 1	3 ± 1	9 ± 2†*	3 ± 1	6 ± 1†
Mean PA pressure (mm Hg)	12 ± 3	37 ± 5†	15 ± 3	51 ± 7†*	13 ± 3	43 ± 8†
PCW pressure (mm Hg)	7 ± 2	22 ± 4†	8 ± 2	31 ± 7†*	6 ± 2	28 ± 5†*

*p < 0.05 percent change of exercise or recovery value from value at rest for the same group; †p < 0.05 normal subjects versus patients with heart failure for the same stage of exercise protocol. F = failure patients; N = normal subjects; PA = pulmonary artery; PCW = pulmonary capillary wedge; RA = right atrial.

failed to increase in patients with heart failure (Fig. 1). During recovery, however, cardiac index rose in patients to a level that was 44% above baseline, whereas it remained 20% higher than the value at rest in normal subjects. At peak exercise, stroke index decreased by 9% below that at rest, and after exercise it increased by 34% above baseline.

Pulmonary capillary wedge pressure in the patient group, which at rest was significantly higher than that seen in normal subjects, increased substantially at peak exercise and remained elevated at 90 s of recovery. The response in right atrial filling pressure of the patients was similar to that observed in wedge pressure (see Table 1).

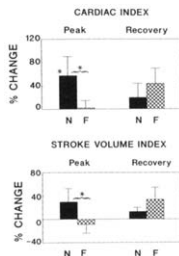
Metabolic and ventilatory responses. Systemic arteriovenous oxygen difference at rest was significantly greater in patients than in normal subjects (Table 2). During peak exercise, the arteriovenous oxygen difference increased fur-

ther in patients, whereas it changed little in normal individuals. On completion of exercise, this variable returned quickly to its value at rest in both groups. Oxygen extraction in the exercising forearm in the patients with heart failure was higher (63 ± 4%) than that (52 ± 3%) in normal subjects, but the difference did not reach statistical significance.

The mixed venous lactate concentration did not differ in patients and normal volunteers at rest; however, it increased significantly during exercise in patients (Fig. 2) and increased further during recovery. In the exercising forearm of patients, venous lactate concentration increased significantly whereas that of the nonexercising forearm remained invariant (Fig. 3, Table 2). Venous lactate in the exercising forearm of normal subjects was also unchanged. This group difference in exercising forearm venous lactate concentration persisted during recovery.

Systemic oxygen uptake was not different between the two study groups at rest or during exercise. During recovery, oxygen uptake rose above exercise levels in patients although it returned to levels at rest in normal individuals (Fig. 4). Carbon dioxide production was equivalent in the two groups at rest and during exercise. However, during recovery, carbon dioxide production increased significantly in patients whereas in the control group it returned to values at rest (Fig. 4). Minute ventilation at rest was significantly higher in the patients than in normal subjects. With exercise, minute ventilation increased by an equivalent degree in both groups. In contrast to normal subjects, patients manifested a further increase in minute ventilation during recovery (Table 2, Fig. 4).

Figure 1. Percent change in cardiac index and stroke volume index of five normal individuals (N) and seven patients with heart failure (F) from baseline to peak exercise and 90 s recovery phases of light isometric forearm exercise. The asterisk denotes a significant change from baseline to peak exercise and the bracketed asterisk indicates a statistically significant difference between normal individuals and patients.



Discussion

The purpose of the study was to monitor the hemodynamic, metabolic and ventilatory responses to light isometric exercise in patients with chronic stable heart failure and to determine whether this form of isometric exercise represented an anaerobic contraction with lactate production in

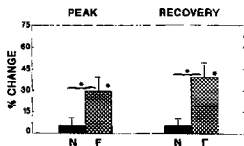
Table 2. Metabolic and Ventilatory Responses to Peak Light Isometric Exercise and 90 s of Recovery in 11 Patients With Heart Failure (F) and 10 Normal Individuals (N)

	At Rest		Exercise		Recovery	
	N	F	N	F	N	F
a-vO ₂ difference (vol %)	5.0 ± 0.4	8.2 ± 0.8†	4.4 ± 0.4	9.8 ± 1.1†	4.7 ± 0.2	8.5 ± 0.8†
O ₂ uptake (ml/min per kg)	254 ± 16	278 ± 18	293 ± 25	353 ± 38	266 ± 29	499 ± 28*†
MV lactate (mg %)	6 ± 0.9	7 ± 0.9	6 ± 0.8	8.4 ± 0.7*†	6 ± 0.7	9 ± 0.7*†
EFA lactate (mg %)	8 ± 4	8 ± 1	9 ± 4	23 ± 2*†	13 ± 4	30 ± 1*†
RFA lactate (mg %)	—	11 ± 2.9	—	10 ± 2.5	—	10 ± 2.6
CO ₂ production (ml/min)	221 ± 15	239 ± 19	292 ± 60	343 ± 39	236 ± 26	385 ± 31*†
V _E (L/min)	9 ± 0.4	15 ± 0.9†	12 ± 2.3	21 ± 3.5†	10 ± 3.5	22 ± 2†

*p < 0.05 percent change of exercise or recovery value from value at rest for the group; †p < 0.05 normal subjects versus patients with heart failure for the same stage of exercise protocol. a-vO₂ = difference in arterial and mixed venous oxygen content (7F and 5N); CO₂ = carbon dioxide (11F and 10N); EFA = exercising forearm (9F and 7N); MV = mixed venous (7F and 5N); O₂ uptake = oxygen uptake (11F and 10N); RFA = nonexercising forearm (4F); V_E = minute ventilation (11F and 10N); — = data not obtained; other abbreviations as in Table 1.

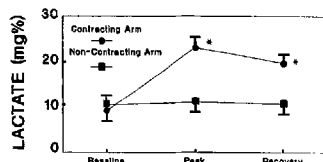
these patients. If this were the case, lactate buffering and carbon dioxide production would lead to an enhanced chemical drive to ventilation that might be responsible for a disproportionate level of ventilation and work of breathing and the appearance of breathlessness. Before we discuss our findings, two potential shortcomings should be identified. The first is the older age (58 ± 12 years) of our patients compared with that (30 ± 10 years) of the normal volunteers. It is not known whether the cardiovascular response to isometric exercise is significantly influenced by aging and, if so, to what degree. Our findings do suggest that light isometric exercise represented an equivalent work load and stress in each group based on the significant increase in heart rate and arterial pressure. Another potential shortcoming is that the cause of heart failure was not uniform in the patient group. However, when the patients were classified by etiology of heart failure (cardiomyopathy or ischemic heart disease), no significant differences in the hemodynamic and metabolic responses to light isometric exercise were noted.

Figure 2. Percent change in mixed venous lactate of five normal individuals (N) and the seven patients with heart failure (F) from baseline to peak exercise and baseline to recovery phases of light isometric exercise. The bracketed asterisk represents a significant difference between the percent change of mixed venous lactate for both groups from baseline to peak and baseline to recovery phases of the isometric exercise. The asterisk indicates a significant percent increase in mixed venous lactate concentration of patients with heart failure from baseline to peak exercise and recovery.



Hemodynamic changes. In contrast to findings in normal subjects and despite a marked increase in left ventricular filling pressure, cardiac index did not increase during exercise in patients with chronic cardiac failure and significant left ventricular systolic dysfunction. A decline in stroke volume was responsible for the invariant cardiac index response to isometric exercise in these patients. Similar findings have been reported by others (1,2,5) and confirm the fact that the failing heart is sensitive to arterial pressure (6) despite an expected increase in myocardial contractility with isometric exercise (7). These findings further underscore the marked limitations in cardiac reserve that exist in the failing heart (3). During recovery, cardiac index returned to values at rest in our normal subjects, whereas it increased in our patient group. Such an increment in cardiac index will normally occur after heavy isometric exercise requiring >30% of maximal voluntary contraction, and for this reason heavy isometric exercise may not be as useful as light isometric exercise in differentiating a patient with abnormal left ventricular systolic function and chronic heart failure from a patient with less impaired systolic function or from a normal subject.

Figure 3. Antecubital venous lactate levels measured in the exercising and nonexercising forearm of four patients with chronic heart failure. The asterisk indicates statistically significant levels of lactate above baseline at peak exercise and recovery.



Mechanisms of metabolic and ventilatory changes. Light isometric exercise normally tends to throttle blood flow to contracting muscles. Compensatory neurologic and cardiovascular reflexes, which include withdrawal of vagal tone and enhanced adrenergic nervous system activity (8), serve to raise arterial pressure by increasing cardiac output and by causing vasoconstriction of nonexercising vascular beds and, thereby, increasing the perfusion of isometrically exercising muscles. A comparable increase in arterial pressure was found in our normal individuals and patients with heart failure. Although cardiac output was not increased in these patients, their arterial pressure was increased, these findings suggest that cardiovascular reflex adjustments were intact and may even have been exaggerated. Nevertheless, the perfusion of exercising muscles was inadequate in these patients, a finding that may be related to their impaired vasodilator reserve (9) and their chronic elevations in systemic vascular resistance (3). Given the inadequate perfusion of exercising muscle, increments in oxygen extraction are needed to sustain their oxygen availability. Exercising forearm oxygen extraction, which includes the venous drainage of nonexercising muscle and the skin, increased to >60% in these patients. Nevertheless, venous lactate concentration of the exercising limb increased significantly, suggesting that oxygen availability was not adequate in exercising muscle. Conversely, venous lactate concentration of the nonexercising forearm in patients was invariant as was that in the exercising forearm in normal volunteers.

Although we did not measure blood flow in the exercising forearm, it is logical to conclude, from the available reported data (9) and our hemodynamic data (that is, reduced cardiac output during exercise), that blood flow to the exercising forearm is reduced during exercise in patients with heart failure. Therefore, less washout and a greater accumulation of the lactate that is generated in the exercising forearm is expected. Nevertheless, in our patients, antecubital venous lactate concentration was markedly elevated during exercise and it continued to be significantly elevated during recovery despite the increase in cardiac output during recovery. These findings suggest an absolute increase in lactate production in the exercising forearm of the patients with heart failure. In normal individuals, forearm blood flow in response to light isometric exercise is known to increase (10). A significant increase in cardiac index in our normal subjects is in keeping with this fact. If lactate production had increased during exercise in the control group, the increase should have been readily detected in the venous blood draining the area. The fact that no increase was observed in our normal group indicates that the delivery of oxygen was adequate to the demand for oxygen. Thus, in patients with heart failure and left ventricular systolic dysfunction, light isometric forearm exercise is both an ischemic and an anaerobic contraction that arises from inadequate perfusion

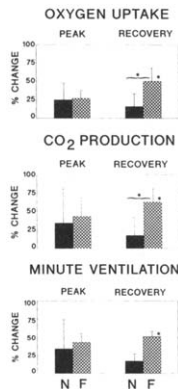


Figure 4. Percent changes in oxygen uptake, carbon dioxide production and minute ventilation at peak exercise and recovery, respectively. The bracketed asterisk denotes a significant difference in percent change of a variable between 10 normal (N) individuals and 11 patients with heart failure (F) during peak exercise and recovery. The asterisk indicates a statistically significant change above baseline in a variable during peak exercise and recovery within a group.

and results in lactate production by exercising forearm muscles.

Mechanisms of enhanced ventilation. The influence of exercising forearm lactate production on ventilation became apparent during the recovery period. Lactic acid is rapidly buffered by bicarbonate (11), resulting in the production of a nonmetabolic source of carbon dioxide that, in turn, stimulates the carotid and aortic chemoreceptors to increase ventilation. The increased carbon dioxide production was evident in our patients during recovery. Concomitantly, the increase in ventilation and increased work of breathing served to increase oxygen uptake during recovery. The increase in ventilation that was observed during exercise in our patients and normal individuals, on the other hand, may have been mediated by metabolic receptors, such as group IV fibers, located in connective tissue and muscle (12-15). The distinctly different ventilatory responses to recovery from light isometric exercise in patients with heart failure and normal individuals may explain why patients perceive themselves to be breathless during or after daily activities that include lifting and carrying loads that require <30% of a maximal voluntary contraction. Further insight into the origin of this limiting symptom, using noninvasive respiratory gas exchange during light isometric forearm exercise in the clinical exercise laboratory, may provide useful informa-

tion with which to judge the severity of failure and the response to therapeutic intervention.

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