CLINICAL STUDIES

Lactate Production During Maximal and Submaximal Exercise in Patients With Chronic Heart Failure

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In patients with chronic heart failure whose cardiac output response to exercise is impaired, determination of anaerobic threshold may provide a useful and objective approach to grade the severity of heart failure. In such patients performing upright treadmill exercise to exhaustion, this study examined the reproducibility of the response of cardiac output and mixed venous lactate concentration when the exercise test was repeated the same or next day, the nature of this response after rest and exercise cardiac output levels were augmented by the cardiotonic agent amrinone and the response of lactate during symptom-limited submaximal exercise performed at either aerobic or anaerobic levels of work for each patient.

Findings were: 1) the response of cardiac output and mixed venous lactate was reproducible (p < 0.05) when assessed either the same or the next day; 2) when exercise cardiac output was increased (p < 0.05) by oral amrinone therapy, the increase in lactate was delayed (p < 0.05) to higher levels of muscular work and this was not true when cardiac output was unchanged; and 3) only submaximal anaerobic exercise was symptom limited and associated with an increase in lactate concentration. Thus, the lactate response and anaerobic threshold determination should prove useful to assess the severity of chronic stable heart failure and its response to pharmacologic intervention. The submaximal anaerobic exercise test may provide additional insights into the effort intolerance these patients experience.

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It is well known that at moderate and severe levels of muscular work, blood lactate concentration is increased (1–3), particularly in the venous blood draining working muscle (4,5). This increase in venous lactate concentration, which indicates the onset of lactate production and presumably a major shift to anaerobic metabolism in working skeletal muscle, was termed the anaerobic threshold by Wasserman and McIlroy (6). We (7) and others (8) suggested that in patients with chronic heart failure, whose cardiac output response to incremental exercise is impaired in proportion to the severity of pump dysfunction, determination of the anaerobic threshold would be a useful clinical tool to grade the severity of heart failure. It is unclear, however, whether the response of venous lactate and cardiac output in such patients is reproducible, whether changes in oxygen delivery would alter the lactate response and whether venous lactate would also increase during prolonged submaximal exercise.

Accordingly, the present study was undertaken in patients with chronic heart failure of varying severity and diverse etiology. Its purpose was to address the following issues: 1) the reproducibility of the response of cardiac output and mixed venous lactate concentration during a standardized, incremental treadmill exercise protocol repeated the same or next day; 2) the nature of the response after oxygen delivery was enhanced pharmacologically by the cardiotonic agent amrinone; and 3) the response of mixed venous lactate during submaximal exercise performed at either aerobic or anaerobic levels of work for each patient.

Methods

Study patients. Sixty-three patients (37 men and 26 women) ranging in age from 15 to 78 years (mean 53 ± 12) and having chronic stable heart failure were included in this study. The etiologic basis of their heart disease included idiopathic congestive cardiomyopathy (36 patients); ischemic heart disease with previously documented myocardial infarction by clinical, electrocardiographic or angiographic criteria (11 patients) and chronic mitral or aortic valve regurgitation (16 patients). The functional status of these patients, representing New York Heart Association clinical classes II to IV, had been stable for at least 2 months before exercise testing. All were outpatients and were main-

tained on digitalis and diuretic drugs for at least 6 months. Nine patients had chronic atrial fibrillation; the remainder were in sinus rhythm. All patients had cardiac enlargement by examination and as estimated by a cardiothoracic ratio of greater than 50% on standard chest roentgenogram.

Patients were excluded if they had angina pectoris requiring treatment with antianginal medications other than occasional use of nitroglycerin, exercise-induced angina, ventricular arrhythmias or significant aortic stenosis or airway disease by standard pulmonary function tests.

Patient selection. The data obtained from all patients whom we have evaluated over the years with invasive hemodynamic monitoring during exercise testing are stored in our Cardio-Pulmonary Exercise Laboratory data bank. Patients included in this report were selected from that bank on the basis of 1) the completion of all of the required exercise tests (analyzed later in this report), 2) complete data files, 3) the severity of disease represented by the spectrum (classes A to D) of heart failure addressed by the analysis, and 4) the etiologic basis of disease (ischemic, myopathic or valvular incompetence as just described).

The initial selection of patients who reexercised on the afternoon of the test day were based solely on the patients' willingness to do so, their successful completion of the morning test and availability of all necessary data (see later) for comparison and determination of reproducibility. The same was true of the cohort performing endurance exercise; however, these patients had to have first completed the incremental test. Patients receiving oral amrinone were selected because they had, on the etiologic basis described, more advanced chronic heart failure that was unresponsive to medical therapy, including digoxin and diuretic drugs.

Incremental exercise. Each patient gave informed written consent to participate in an experimental protocol approved by the hospital's review board. On the morning of the study and 2 to 3 hours after a simple liquid breakfast, a triple lumen flotation catheter was advanced into the pulmonary artery through an antecubital vein. Patients were then taken to the air-conditioned (21 to 23°C) exercise facility where their hemodynamic response to incremental treadmill exercise was monitored together with the breath by breath respiratory gas exchange, air flow, mixed venous lactate concentration and oxygen saturation responses.

The incremental treadmill exercise program consisted of 2 minute stages of progressive work. The exercise protocol, reported elsewhere (9), was designed to accommodate the wide range of aerobic capacities seen in patients with chronic heart failure. Each patient had previously performed one or more exercise tests and therefore was familiar with the treadmill protocol. As previously reported (7), intravascular pressures, cuff blood pressure, a modified lead V_5 electrocardiogram and heart rate were monitored at rest, throughout exercise and during recovery. Cardiac output was determined by the Fick principle from the oxygen uptake ($\dot{V}O_2$,

ml/min) measurement and the calculation of the arteriovenous oxygen difference.

The data acquisition protocol was as follows: hemodynamic data, mixed venous lactate concentration, oxygen saturation, respiratory gas exchange and air flow data were obtained with the patient standing quietly for several minutes. During exercise, end-expiratory wedge pressure was obtained at the midpoint of each stage of exercise while mixed venous blood was sampled during the last minute of each stage.

Patients were exercised to exhaustion and to their maximal oxygen uptake ($\dot{V}O_2$ max), as defined by $\dot{V}O_2$ changing less than 1 ml/min per kg despite an increment in work load that was sustained for 30 seconds or longer. As previously reported (7), we grade the severity of chronic heart failure according to $\dot{V}O_2$ max as follows: greater than 20 ml/min per kg represents no to mild heart failure (class A, 5 patients); 16 to 20 ml/min per kg, mild to moderate failure (class B, 7 patients); 10 to 15 ml/min per kg, moderate to severe failure (class C, 25 patients) and less than 10 ml/min per kg, severe failure (class D, 26 patients).

Mixed venous blood was immediately analyzed for lactate concentration (Yellow Springs YSI 23L). This technique was validated by its comparison with a standard spectrophotometric method (10). The normal lactate value at rest for this laboratory was 7.24 ± 1.63 mg/100 ml. The onset of lactate production by exercising skeletal muscle was considered to be present when mixed venous lactate concentration exceeded 12 mg/100 ml (average value at rest ± 2 SD). For the analysis of anaerobic threshold for each exercise class, the $\dot{V}O_2$ corresponding to this increase in mixed venous lactate was selected (Fig. 1).

Reproducibility. The response of hemodynamics, mixed venous lactate and $\dot{V}O_2$ to incremental exercise was determined in all 63 patients. After a recovery period of at least 2 hours, eight of these patients were reexercised. The protocol for the same day exercise study was similar to that outlined. In addition, 20 other patients were reexercised the next day after they had received oral amrinone (1.64 ± 0.18 mg/kg body weight every 8 hours for four doses), a cardiotonic agent with positive inotropic and vasodilator properties.

Submaximal endurance exercise. After anaerobic threshold and $\dot{V}O_2$ max were determined, nine other patients were reexercised after a recovery period of 1 or more hours. In these patients, the second exercise test consisted of submaximal endurance exercise at a work load that was selected from the incremental test as representing aerobic (five patients) or anaerobic (four patients) exercise for that patient. The patients were instructed to exercise at this work load until symptomatic and unable to continue or until 20 minutes had elapsed, at which time the test was electively terminated. Exercise hemodynamics and mixed venous blood for oxygen and lactate were sampled every 3 minutes while

Figure 1. The response in mixed venous lactate concentration and oxygen utilization ($\dot{V}O_2$) in patients standing at rest and for each stage of exercise is shown (mean ± SD) for the five functional classes of patients with chronic heart failure. Classes A to E indicate heart failure of increasing severity from mild to very severe. Lactate production was considered present when mixed venous lactate concentration exceeded 12 mg/100 ml (**dashed line**).
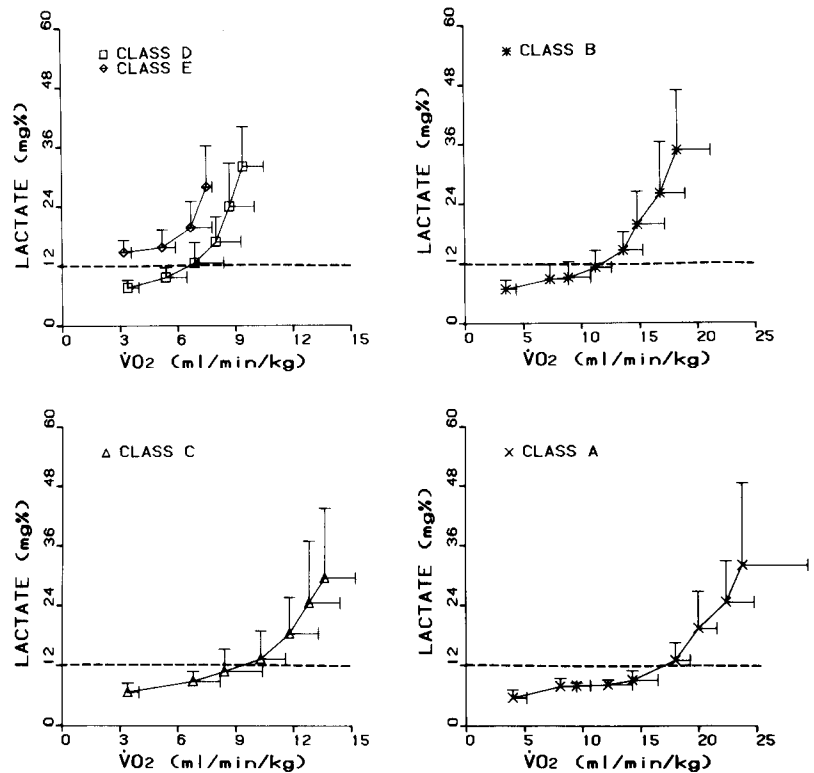
respiratory gas exchange and the ventilatory response were monitored continuously.

Statistical analysis. Patients were grouped on the basis of their $\dot{V}O_2$ max and all combined results are presented as mean ± SD. Reproducibility was assessed by paired data analysis. For each patient and each level of exercise, including values at rest, morning (AM) results were compared with afternoon (PM) data and day 1 with day 2. Pre-amrinone (control) and post-amrinone (32 hour) results were compared at each exercise stage with each patient serving as his or her own control. To ascertain whether, at any given level of work, there was a statistically significant difference in the hemodynamic response to exercise for the control period or after amrinone administration, a paired t test was used. Finally, comparisons of regression line slopes and intercepts were made using the method outlined by Brownlee (11). Submaximal aerobic and anaerobic exercise groups were compared at rest or at any given level of exercise using the one factor analysis of variance and the modified t statistic (12). Minimal acceptable significance for all statistical tests was a probability value less than 0.05/k, where k is the number of comparisons performed (12).

Results

Lactate production at rest and during incremental exercise. In four class D patients (severe heart failure), mixed venous lactate concentration at rest exceeded 12 mg/100 ml (range 12.5 to 18.1). The average cardiac output at rest,

left ventricular filling pressure and oxygen extraction for these four patients was 1.49 ± 0.56 liters/min per m², 24 ± 5 mm Hg and 52 ± 8%, respectively. During incremental treadmill exercise their cardiac output increased to a maximum of only 2.09 ± 0.59 liters/min per m², whereas wedge pressure and oxygen extraction reached 33 ± 5 mm Hg and 75 ± 6%, respectively; $\dot{V}O_2$ max was 7.07 ± 1.43 ml/min per kg. Because oxygen delivery at rest was inadequate to sustain oxidative metabolism in these patients, we added another category, class E, to our classification of heart failure and considered these four patients as having very severe heart failure.

In the remaining 59 patients, representing mild to severe heart failure, or classes A to D, anaerobic metabolism did not commence until oxygen demand had increased with exercise. The response in mixed venous lactate concentration as $\dot{V}O_2$ increased with each stage of progressive treadmill exercise is shown for classes A to E in Figure 1. It is apparent that as the severity of heart failure increased, the onset of anaerobic metabolism, or anaerobic threshold (defined as mixed venous lactate of greater than 12 mg/100 ml) occurred at a progressively lower $\dot{V}O_2$. In classes A to D, the anaerobic threshold was 19.0 ± 4.4, 11.9 ± 3.3, 9.3 ± 2.5 and 6.5 ± 2.0 ml/min per kg, respectively. In each class the $\dot{V}O_2$ at the onset of anaerobiosis represented approximately 70% of $\dot{V}O_2$ max.

Reproducibility of lactate production during incremental exercise. *Same day.* The responses of cardiac output and mixed venous lactate concentration on the morning

test were quite reproducible when reexamined on the afternoon of the same day in eight patients (one in class B, two in C, four in D and one in E) (Fig. 2).

Next day. In all 20 patients receiving oral amrinone for 32 hours (or four half-lives of the drug), the response of ventricular function to exercise was improved on the repeat exercise test. Left ventricular filling pressure was significantly ($p < 0.05$) reduced at each stage of exercise while the response of exercise cardiac output was either similar to that of day 1 baseline in 8 patients (1 in class B, 3 in C and 4 in D) or significantly ($p < 0.05$) increased in 12

patients (1 in class B, 5 in C and 6 in D). These responses were then separated according to whether the exercise cardiac output was increased or unchanged after amrinone administration. The cardiac output and lactate data for days 1 and 2 are given for each of these responses to amrinone in Figures 3 and 4. It is apparent that with augmented systemic blood flow during exercise (average increase of 9% or a slope of 1.09; upper panel, Fig. 3), lactate production was retarded on day 2 (lower panel) with the slope of 0.55 being significantly ($p < 0.05$) less than that for the line of identity (slope = 1.00). The increase in mixed venous lactate to greater than 12 mg/100 ml was delayed by at least one stage of exercise. In patients whose cardiac output re-

Figure 2. Rest and exercise cardiac index and mixed venous lactate concentration data obtained in the morning (AM) are compared with similar data obtained in the afternoon (PM) from the same patient. Reproducibility data from eight patients are presented. The **solid line** is the regression line with slope M, N is the number of data points and R is the correlation coefficient. Classes B to E designate the severity of heart failure (see text). This format is also used in Figures 3 and 4.
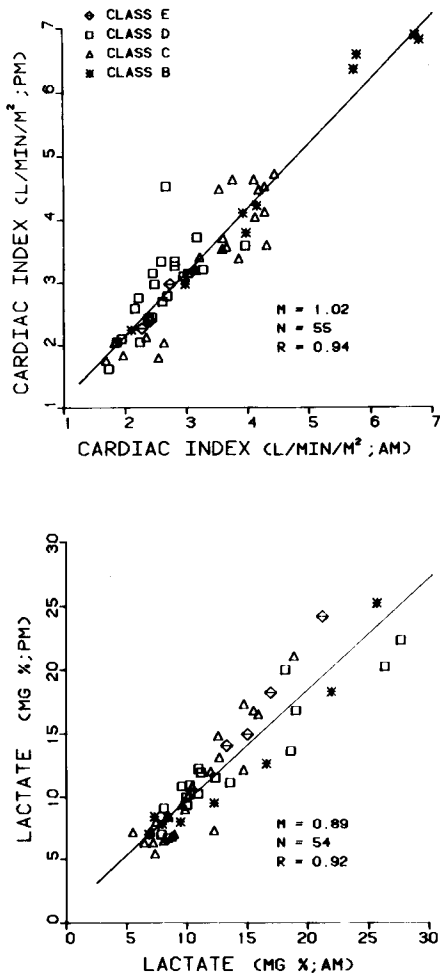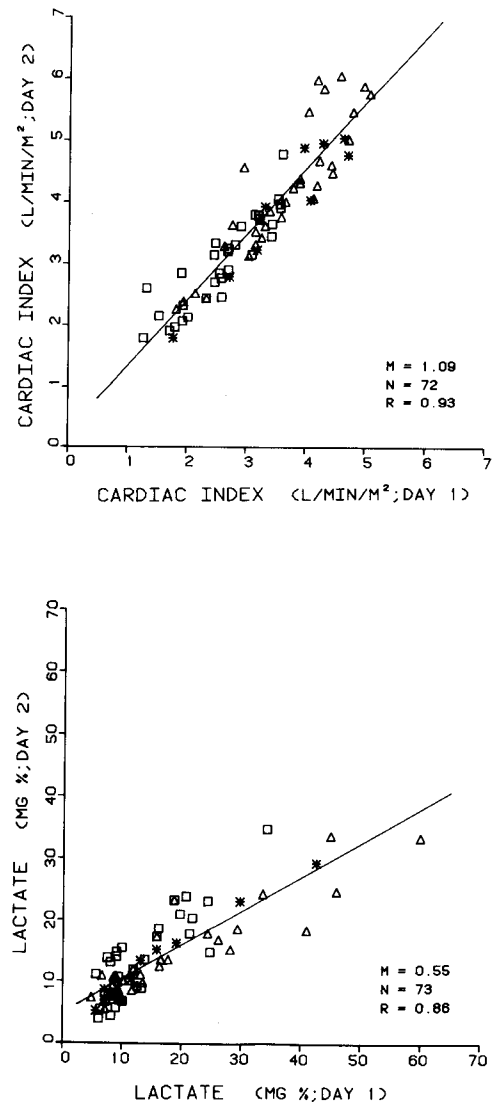
Figure 3. After 32 hours of amrinone therapy, the cardiac output response to exercise was significantly increased in 12 patients (slope 1.09; **upper panel**). The response in mixed venous concentration to exercise in these patients was improved in that lactate levels were lower after amrinone administration (slope 0.55; **lower panel**). Abbreviations as in Figure 2.

sponse to exercise was unchanged from baseline after amrinone administration (upper panel, Fig. 4), the lactate response on day 2 (lower panel) was no different from that on day 1.

Lactate production during aerobic and anaerobic endurance exercise. The five patients performing steady state ($\dot{V}O_2 \pm 2\%$) *aerobic* endurance treadmill exercise were able to complete the full 20 minute protocol. The level of work represented $60 \pm 3\%$ of their $\dot{V}O_2$ max. These patients experienced no symptoms of fatigue or breathlessness and their exercise was electively terminated. The average standing cardiac output of these patients was 2.12 ± 0.31 liters/min per m^2, which increased to 3.90 ± 1.6 liters/min per m^2 during submaximal exercise (Fig. 5). The standing rest to

Figure 4. After 32 hours of amrinone therapy, the cardiac output response to exercise was unchanged in eight patients (**upper panel**). Their lactate response to exercise was also unchanged (**lower panel**). Abbreviations as in Figure 2.
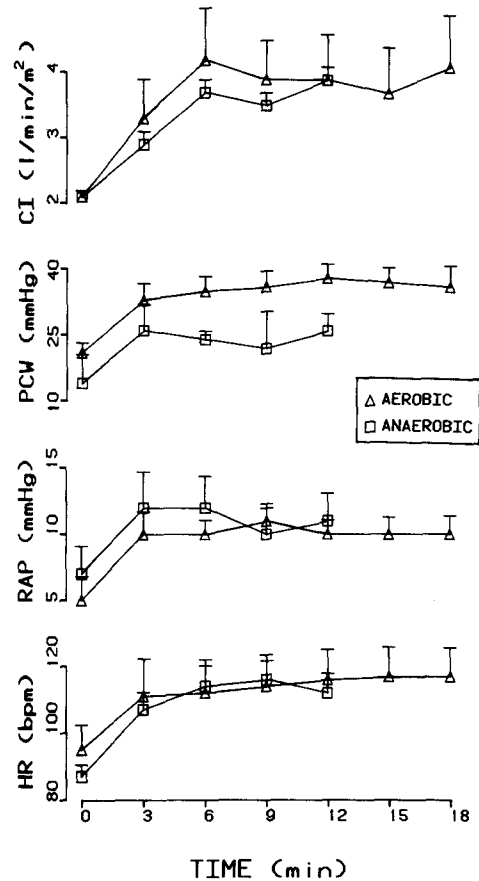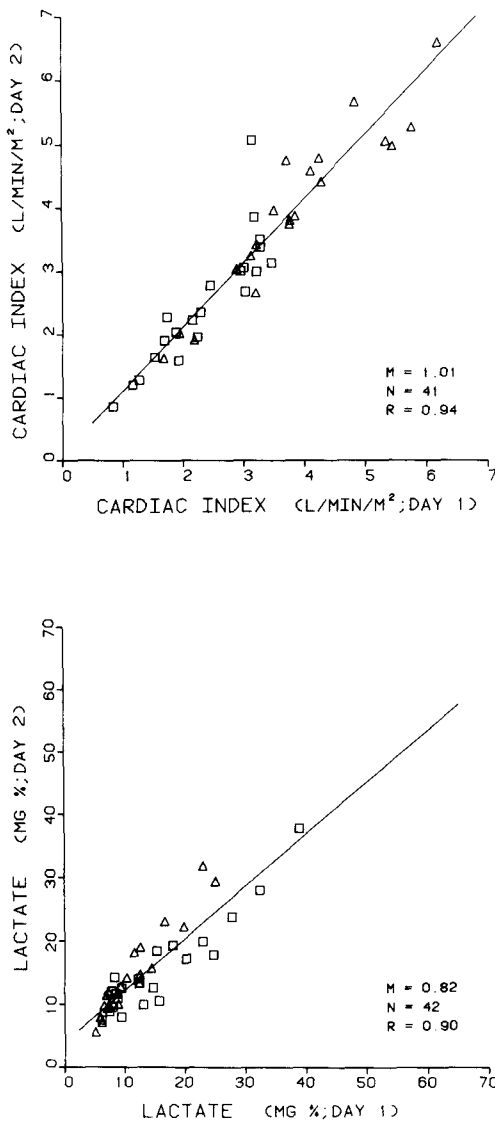

Figure 5. The average hemodynamic and heart rate response to submaximal aerobic (five patients) and anaerobic (four patients) endurance exercise. Shown are standing rest data and data obtained at 3 minute intervals of constant level exercise for cardiac index (CI), pulmonary wedge pressure (PCW), right atrial pressure (RAP) and heart rate (HR).

end-exercise increases in wedge pressure (21 ± 5 to 36 ± 8 mm Hg), heart rate (95 ± 17 to 117 ± 19 beats/min) and right atrial pressure (5 ± 4 to 10 ± 3 mm Hg) are also shown in Figure 5. Mixed venous lactate, which was 6.48 ± 3.06 mg/100 ml at rest, was unchanged during exercise (Fig. 6). From its level at rest of 17 ± 3 liters/min, minute ventilation increased to a steady state of 31 ± 6 liters/min with aerobic exercise (Fig. 6). Shown in Figure 7 are the components of the ventilatory response to aerobic endurance, which consisted of a steady state increase in respiratory rate from 22 ± 3 beats/min at rest to 28 ± 5 beats/min with exercise and tidal volume, which increased from 762 ± 181 ml at rest to $1,150 \pm 170$ ml with exercise.

For the four patients who performed steady state anaerobic endurance exercise at $92 \pm 4\%$ of their $\dot{V}O_2$ max, the hemodynamic response was not significantly different from that of their counterparts performing aerobic exercise (Fig. 5). Cardiac output increased from 2.10 ± 0.17 liters/min per m^2 at rest to 3.85 ± 0.21 liters/min per m^2 with exercise; wedge pressure and right atrial pressure increased from 14
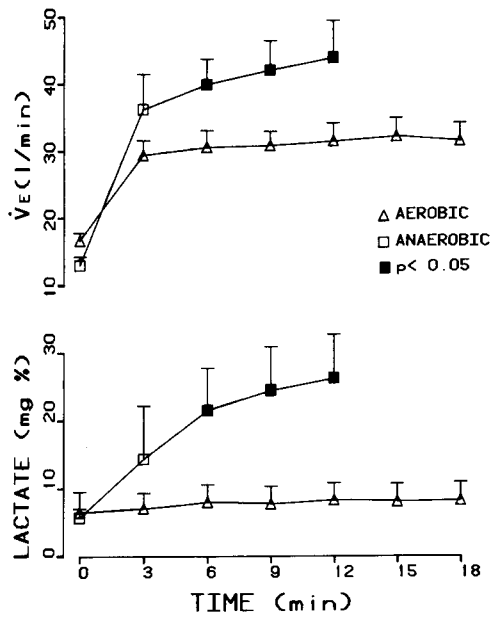
Figure 6. The response of mixed venous lactate concentration and minute ventilation ($\dot{V}_E$) during submaximal aerobic and anaerobic endurance exercise.

$\pm$ 11 and 7 $\pm$ 7 mm Hg at rest to 25 $\pm$ 6 and 12 $\pm$ 8 mm Hg, respectively, with exercise. Heart rate was similarly increased from 87 $\pm$ 7 to 115 $\pm$ 12 beats/min with anaerobic exercise. A progressive increase in mixed venous lactate was seen with anaerobic endurance exercise. Figure 6 depicts the increase in lactate that reached 26.39 $\pm$ 6.51 mg/100 ml with anaerobic exercise from its level at rest of

Figure 7. The response of tidal volume (V_T) and respiratory rate (f) to submaximal aerobic and anaerobic endurance exercise.
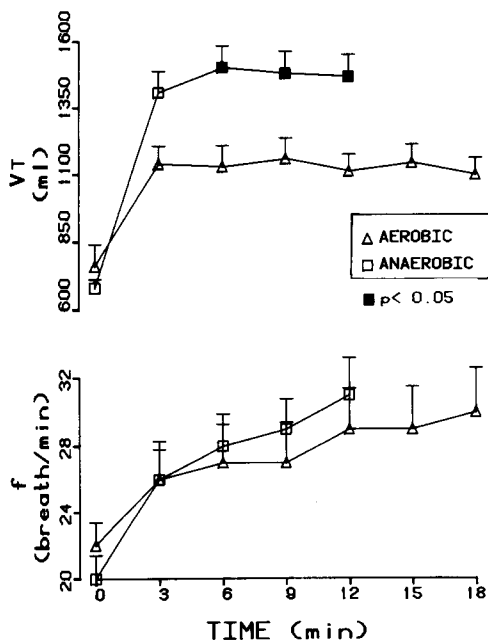
5.70 $\pm$ 1.38 mg/100 ml. Moreover, these patients experienced either dyspnea or fatigue as their dominant symptom, which was perceived to be of sufficient severity to prematurely terminate (10.6 $\pm$ 3.8 minutes) the 20 minute endurance test. As a result of the progressive increase in lactate there was a different ventilatory response to exercise characterized by a progressive increase in minute ventilation (Fig. 6) from 13 $\pm$ 3 liters/min at rest to 44 $\pm$ 11 liters/min at end-exercise. The increase in minute ventilation was achieved by a steady increase in tidal volume from 682 $\pm$ 64 to 1,470 $\pm$ 360 ml and a progressive increase in respiratory rate from 19 $\pm$ 3 beats/min at rest to 31 $\pm$ 4 beats/min at end-exercise.

Discussion

During physical work, the oxygen requirements and carbon dioxide produced by muscle are both increased. Normally the ventilatory response does not limit the transfer of oxygen to hemoglobin or the elimination of carbon dioxide during maximal exercise (13,14); this is also true in patients with chronic heart failure (7). The heart, on the other hand, has a given capacity to deliver oxygenated blood to the metabolizing tissues. Maximal cardiac output, together with maximal oxygen extraction by the tissues and regional blood flow, determines the aerobic capacity of skeletal muscle. Because tissue oxygen extraction is not impaired in these patients (7), the response in cardiac output is central to regulating their aerobic capacity (7). In the absence of a training effect, where the distribution of blood flow or oxidative capacity of skeletal muscle may be increased (15) over many weeks of exercise, the anaerobic threshold will also be determined by exercise cardiac output.

Oxygen delivery and anaerobic metabolism. We have previously demonstrated (7,16) that patients with heart disease have an abnormal augmentation in cardiac output response to exercise. In fact, the maximal cardiac output attained during exercise can be predicted by noninvasively determining the maximal oxygen uptake ($\dot{V}O_2$ max). Under these circumstances, when oxygen delivery is inadequate to satisfy the prevailing demand for oxygen, anaerobiosis begins with a major shift of intracellular redox systems toward their reduced form. As a result, lactate production increases in working muscle, whether it is skeletal muscle (1–3) or the heart (17,18). The increase in blood lactic acid during exercise has been used to reflect such a defect in oxygen delivery to working skeletal muscle. As early as 1927, Meakins and Long (19) noted that during standing/running or walking the lactic acid concentration of peripheral venous blood was greater in patients with rheumatic mitral valve disease than in normal subjects. Moreover, in patients with very severe heart failure, venous lactate was increased at rest and increased even further with a deterioration of the patient's symptomatic failure and to an extent that corre-

sponded with the severity of the circulatory impairment. Hallock (20) confirmed these findings during exercise with a chair ergometer in patients with valvular and congenital heart disease and also noted that the increase in venous lactic acid was most pronounced in the presence of a right to left shunt.

In a large group of patients with rheumatic valvular heart disease, Donald et al. (4) demonstrated the profound levels of oxygen extraction achieved by working skeletal muscle and the increase in femoral vein lactate concentration associated with submaximal levels of supine leg exercise. They also observed that the more severe the impairment in exercise cardiac output, the earlier the onset of anaerobic metabolism. Similar observations were reported during upright ergometry by Wilson et al. (5) in patients with heart failure secondary to myopathic or ischemic heart disease. Thus, the severity of heart failure can effectively be graded by the appearance of anaerobic metabolism during exercise or, in extreme cases (for example, class E patients), at rest. We (7) previously confirmed the relation between the appearance of lactate production and aerobic capacity during upright treadmill exercise in patients with chronic heart failure of moderate to marked severity, as did Matsumura et al. (8).

Reproducibility of the lactate response. In this study we have extended these observations to include mild and very severe heart failure. Moreover, we have indicated the reproducibility of the response in mixed venous lactate concentration during progressive upright exercise measured the same or next day and its relation to the response in exercise cardiac output. The present observations on anaerobic threshold determined from the increase in mixed venous lactate concentration greater than 12 mg/100 ml correlate with our previously reported (7) findings using noninvasive respiratory gas exchange techniques. Irrespective of the severity of heart failure, however, lactate production was observed to begin when 60 to 70% of VO_2 max had been achieved.

Lactate and alterations in oxygen delivery. In this study, the acute pharmacologic improvement in ventricular function and exercise cardiac output seen with amrinone augmented the aerobic capacity and delayed the appearance of anaerobic metabolism during exercise. Similar findings were reported by Siskind et al. (21). The improvement in oxygen delivery seen with dobutamine (22,23) or hydralazine (24,25), however, has not been associated with an enhanced aerobic capacity or delayed lactate response. These latter findings can presumably be attributed to a shunting of blood away from working muscle that is secondary to the accompanying pharmacologic vasodilation. An improvement in aerobic capacity and presumably exercise cardiac output has also been observed after surgical treatment of mitral stenosis (26,27) and congenital heart disease (28). The long-term treatment of chronic heart failure with blockade of the postsynaptic

alpha receptor by trimazosin (9) has also been reported to be associated with a delay in the appearance of anaerobic metabolism, although here the additional influence of training may have been operative as a patient's functional status improved, permitting greater symptom-free physical activity. Training was shown to delay lactate production in both normal subjects (29) and patients with heart disease (15). However, we did not observe such a response in anaerobiosis in long-term controlled trials where hydralazine (30) or the beta-adrenergic receptor agonist pirbuterol (31) was compared with placebo. Moreover, it is doubtful that an acute training response was operative in this study.

Thus, the delay in anaerobic threshold observed in response to any pharmacologic intervention will be based on a group of factors, including an improvement in systemic blood flow and specifically nutritive blood flow to working skeletal muscle, and the training response within skeletal muscle and its circulation.

Lactate and the ventilatory response to submaximal exercise. Our findings indicate that in patients with chronic stable heart failure of varying severity, submaximal aerobic endurance exercise of 20 minutes' duration is not accompanied by an increase in mixed venous lactate concentration. As a result, a steady state ventilatory response is observed and patients experience no sense of breathlessness or fatigue. Similar findings were reported for normal subjects (3,32). The lack of objective and quantitative end points to submaximal aerobic exercise would appear to limit its usefulness in the evaluation of heart failure. In contrast, submaximal anaerobic endurance exercise is associated with a progressive increase in venous lactate, a nonsteady state ventilatory response and the sensation of dyspnea in these patients. This type of submaximal exercise may have clinical application to the evaluation of exertional dyspnea. In patients having previous carotid body resection for asthma, the ventilatory response to anaerobic exercise was much delayed and blunted (32). Thus, because exercise pulmonary venous pressure was not significantly different in both forms of submaximal exercise, it is tempting to speculate that the sensation of exertional dyspnea in patients with heart or circulatory failure is mediated through the carotid bodies and not from within the lung and its receptors. This view, however, remains to be tested. At least the appropriate exercise modality to evaluate ventilatory control in patients with heart failure is apparent.

Limitations of the study. Finally, the limitations of the present study should be considered. We did not measure femoral vein lactate or the lactate concentration of leg muscle. Their relation to the measurement of mixed venous lactate will have to be considered in future studies. This is particularly relevant to examining the issues of lactate production, lactate release and lactate clearance in muscle and their relation to the anaerobic threshold determination. Our findings nevertheless strongly suggest that oxygen delivery

and availability are important factors in the overall process of lactate production that occurs during exercise in patients with chronic heart failure. In normal subjects other factors, such as skeletal muscle fiber type, capillary density or glycolytic enzyme composition (33), may be of greater importance. Finally, the measurement of mixed venous lactate concentration used in this study may be more appropriate to examining the timing and the coupling of the ventilatory response to lactate production, given the presumptive role of the carotid bodies in mediating this response.

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