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Exercise Gas Exchange in Heart Failure: Central and Peripheral Factors

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Introduction

In recent years, attention has been directed at the mechanism for exercise intolerance in patients with chronic heart failure (HF). Chronic HF is associated with impaired myocardial function which limits the heart's ability to increase cardiac output in response to exercise to the level normally required (central factor)[1~4]. However, recent experimental work demonstrated that the skeletal muscle is abnormal in chronic HF patients (peripheral factor)[5~10] and this might account for the limited ability of HF patients to exercise. The peripheral factors that have been described take two forms.

One is a reduction in aerobic enzymes which impairs the rate of substrate flow through the tricarboxylic acid cycle and therefore the rate of high energy phosphate regeneration needed for exercise[5,8]. The second is a change in fiber type distribution from type 1 (high density of mitochondria and therefore high oxidative capacity) to type 2b (low density of mitochondria and therefore low oxidative capacity)[6,8,10]. These changes have the potential to impair the rate of increase in O_2 consumption ($\dot{V}O_2$) and thereby the rate of regeneration of the high energy phosphate required to perform exercise.

Both peripheral and central factors should impair the increase in O_2 consumption required to perform exercise and cause lactate to increase at a work rate below that normally observed as illustrated in figure 1. However peripheral factors imply that the cell is deficient in mitochondria or enzymes required to utilize O_2 in the bioenergetic process (Fig. 2). In con-

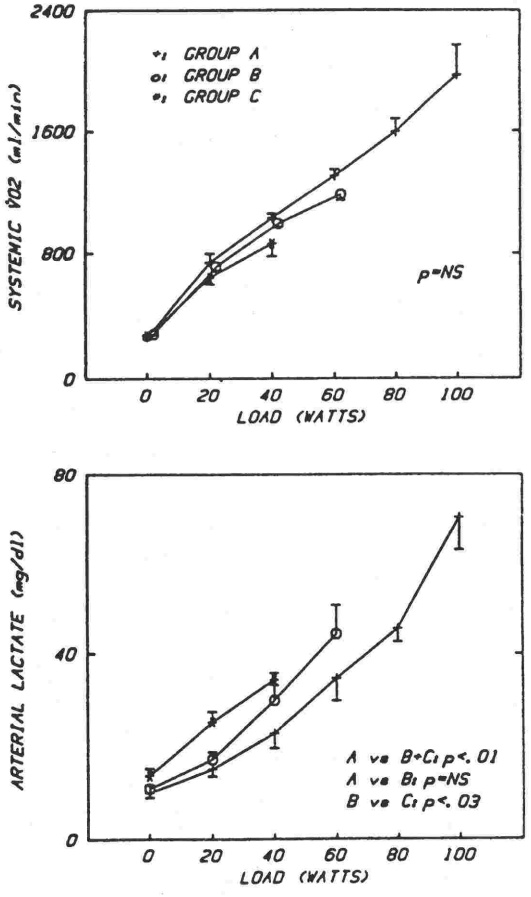

Figure 1 O_2 uptake (upper panel) and lactate (lower panel) as related to work rate for heart failure patients according to severity of disease. (From Wilson et al, Reference 1)

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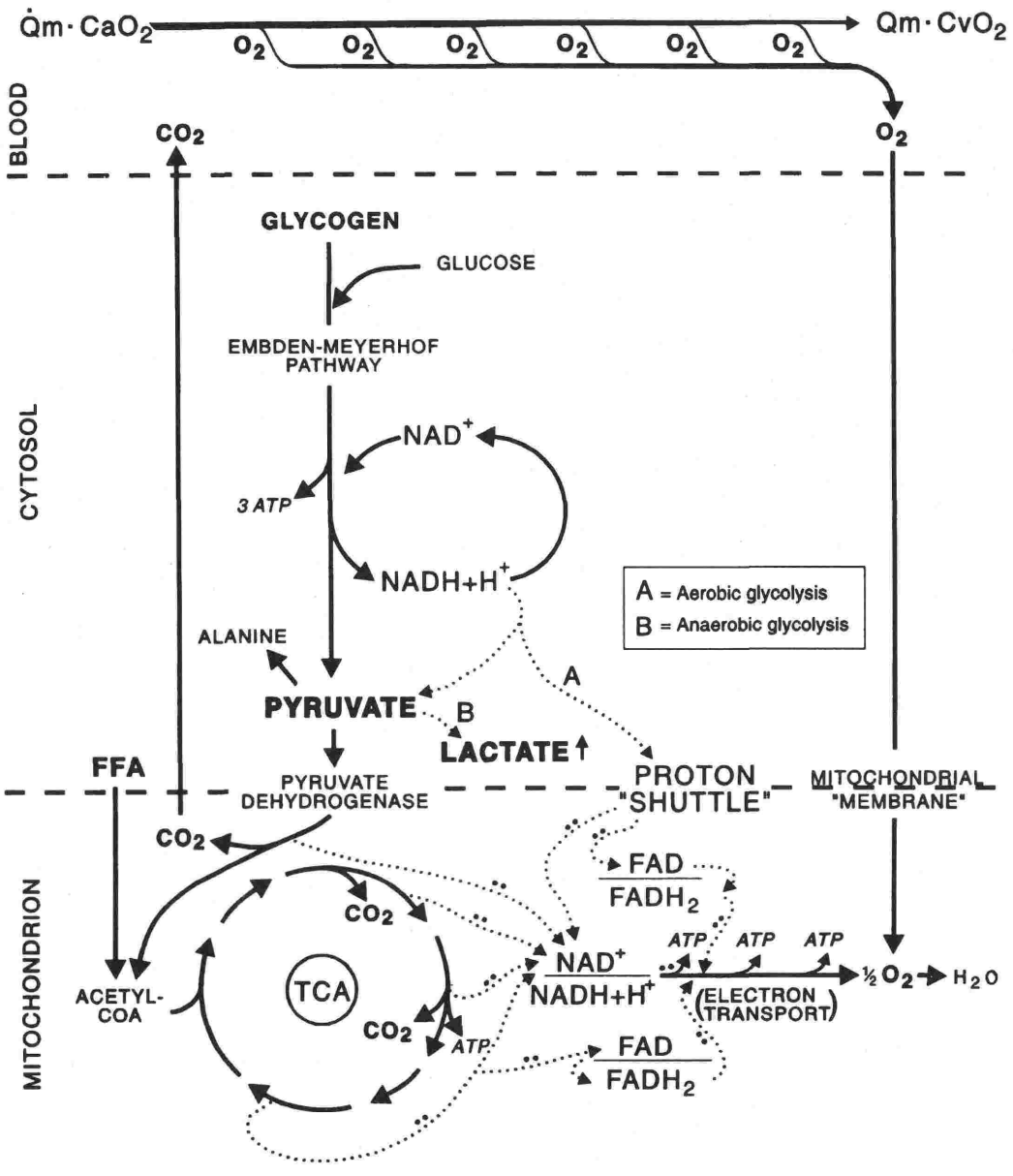

Figure 2 Pathways for O_2 utilization in high energy phosphate (ATP) production. The pathway for aerobic glycolysis (pathway A) provides substrate to the tricarboxylic acid (TCA) cycle without an increase in lactate because cytosolic $NADH+H^+$ is reoxidized by mitochondrial membrane shuttles, mitochondrial coenzymes, the electron transport chain, and molecular O_2. During anaerobic glycolysis (pathway B), pyruvate reoxidzes cytosolic $NADH+H^+$ to NAD^+ with production of lactate. Since lactate does not accumulate for exercise below the lactic acidosis threshold (LAT), glycolysis takes place aerobically. Above the LAT work rate, lactate concentration increases relative to pyruvate, indicating a change in cytosolic redox state and an increase in $NADH+H^+/NAD^+$ ratio. The induction of anaerobic glycolysis and reduction in O_2 utilization can occur early if O_2 transport to the mitochondria were impaired (central factor), or if the rate of electron production by the TCA cycle were inadequate to supply the electron transport chain with the electrons required for the work performed (peripheral factor). FFA, free fatty acid; Lac, lactate; Pyr, pyruvate; Qm, muscle blood flow; Ca_{O_2}, arterial O_2 content; Cv_{O_2}, venous O_2 content.

trast, central factors imply that O_2 utilization is limited by a deficient O_2 transport mechanism, but the bioenergetic machinery in the muscle is capable of extracting O_2 from the capillary blood and generating high energy phosphate (Fig. 2), normally.

Because $\dot{V}O_2$ is equal to cardiac output x arterial-mixed venous O_2 difference [C(a-v)O_2], the decreased $\dot{V}O_2$ at maximal exercise (Fig. 1) can be caused by the heart's inability to respond to the increased energetic requirement of the muscle (central factor, cardiac output increase) with C(a-v)O_2 increasing normally. In contrast, the decreased $\dot{V}O_2$ for maximal effort exercise may be due to the inability of the skeletal muscle to utilize O_2 from the flowing blood because of deficient oxidative enzymatic reactions for electron production or deficient mitochondria in skeletal muscles. This would slow regeneration of high energy phosphate and prevent the normal extraction of O_2, resulting in a relatively low peak C(a-v)O_2 at maximal effort exercise. Thus the degree to which O_2 can be extracted from the capillary blood by the muscle (C(a-v)O_2) at maximal effort exercise should reveal whether decreased O_2 transport or a skeletal muscle defect is the primary factor limiting exercise performance. The peripheral factor should reduce O_2 extraction and peak $\dot{V}O_2$. The central factor should be accompanied by a high or normal O_2 extraction with a reduced peak $\dot{V}O_2$. The question to be addressed in this paper is whether the experimental findings in gas exchange support the central or peripheral mechanisms for the reduced aerobic function ($\dot{V}O_2$) and exercise performance in chronic HF patients.

Experimental observations

$\dot{V}O_2$ in response to exercise in chronic heart failure as compared to normal :

A number of studies have demonstrated that $\dot{V}CO_2$ starts to increase in response to increasing work rate exercise with a similar slope to normal but, before the subject fatigues, the $\dot{V}O_2$ fails to increase normally[1~3]. This is associated with an increased blood lactate concentration as compared to the response of control, healthy subjects (Fig 1). Constant work rate studies further clarify the differences between chronic heart failure patients and control subjects with respect to the abnormal gas exchange response[11~13]. As shown in figure 3, the rate of increase in $\dot{V}O_2$is slow and the $\dot{V}CO_2$ response is increased in the chronic HF patients. The increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ indicates that the failure to consume O_2 at the normal rate is associated with increased lactic acid production. As HCO_3 buffers the H^+ produced with lactate, CO_2 is released. This extra CO_2 reflects anaerobic metabolism[14]. These abnormal metabolic responses are associated with an increase in the ventilatory and heart rate responses compared to that of the healthy subject (Fig. 3). The mechanisms for these altered responses are discussed elsewhere[13,15],

Scheme showing mechanism linking O_2 extraction to high energy phosphate (ATP) production:

Oxygenated blood is delivered to the muscle capillary bed during exercise at an increased rate. The purpose is to allow high energy phosphate to be produced aerobically, as shown in figure 2. The O_2 consumed is determined by the rate of activity of the muscle mitochondria and the O_2 supply. Because the blood entering the muscle has a high PO_2 (about 90mmHg at sea level), O_2 supply is always adequate for the myocyte at the arterial end of the capillary (Fig. 4). However, simple mass balance equations reveal that the rate of decrease in the capillary blood PO_2 depends on the ratio of O_2 supply to the O_2 consumption, as shown in figure 4. The fall in PO_2 along the capillary bed, as blood traverses the capillary bed from artery to vein and assuming that O_2 is consumed at a constant rate (Fig. 4), can be calculated by referring to oxyhemoglobin dissociation curves, allowing for a Bohr effect due to aerobic CO_2 production.

Because each liter of blood with a hemoglobin concentration of 15 gm/dl contains only 200 ml of O_2, to walk at a rate requiring 1 liter of $\dot{V}O_2$, 5 liters of blood must theoretically be delivered to the exercising muscles each minute. However this would require

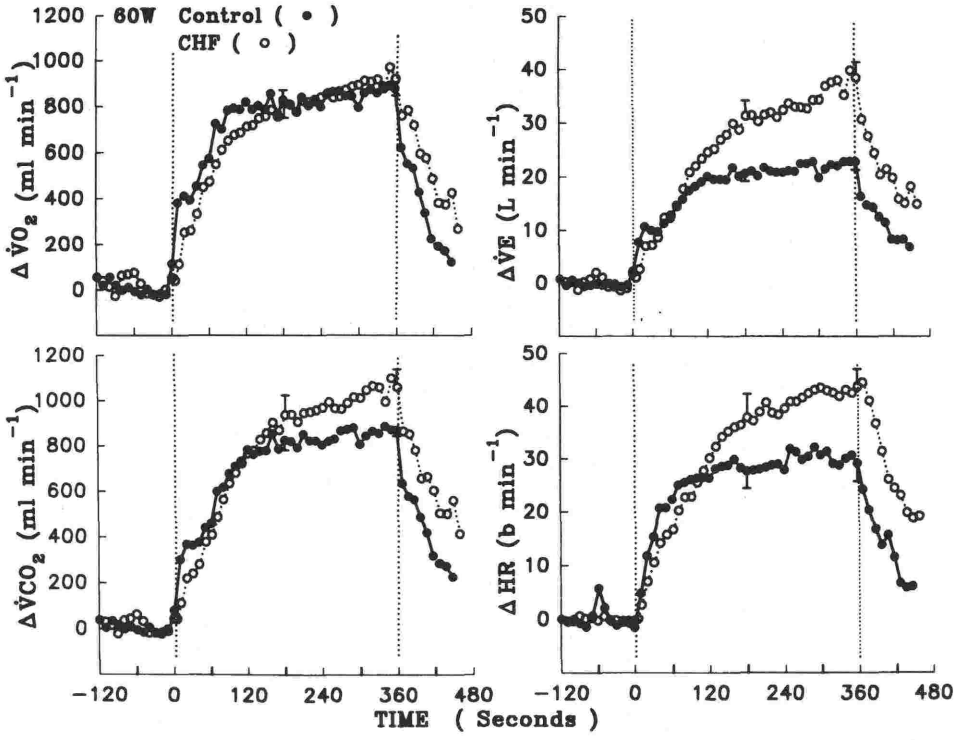

Figure 3 Average increase in oxygen uptake ($\Delta \dot{V}O_2$), CO_2 output ($\Delta \dot{V}CO_2$), minute ventilation ($\Delta \dot{V}E$) and heart rate (IHR) for 18 CHF patients (open circles) and 10 age, size and gender matched healthy subjects (solid circles) for 60w cycle ergometer exercise. The data are calculated breath-by-breath and interpolated second-by-second. After time-aligning the measurements to the start of exercise, the second-by-second measurements were averaged every 10s for each subject and then averaged for the group. The vertical bars at 180 and 360s are the standard deviations at those times. (From Wasserman et al, Reference 13)

some anaerobic metabolism toward the venous end of the capillary bed because it is not possible to extract all of the O_2 from the capillary blood. A PO_2 gradient is needed between the red cell and myocyte for O_2 to flow from the capillary to the mitochondrion over the entire length of the capillary bed. Experimental studies have shown that the minimum end capillary PO_2 (critical capillary PO_2) is reached at the lactate threshold (Fig. 5) and this critical capillary PO_2 is about 16-22 mmHg in normal subjects[16]. Thus at least 6 liters of leg blood flow would be needed for a leg O_2 consumption of 1 liter/min as shown in figure 4. Added to the blood flow needed by the other organs of the body, walking without a lactic acidosis would require at least 10 to 11 L/min cardiac output in a normal sized adult.

The argument posited by advocates of the peripheral mechanism limiting exercise is that $\dot{V}O_2$ does not increase appropriately because there is a defect in muscle aerobic capacity and not a defect in O_2 transport. Studies by Lewis et al[17,18] show that a defect in the glycolytic pathway, in which the increase in glycolysis is inadequate to supply substrate to the tri-carboxylic acid cycle, results in a reduced rate of O_2 extraction as compared to normal, at maximal exercise. The O_2 extraction from blood during maximal exercise is consequently reduced in enzyme defects of the glycolytic pathway[17,18] as well as the electron transport chain[19]. In response to these enzymatic defects of cellular bioenergetics, the cardiac

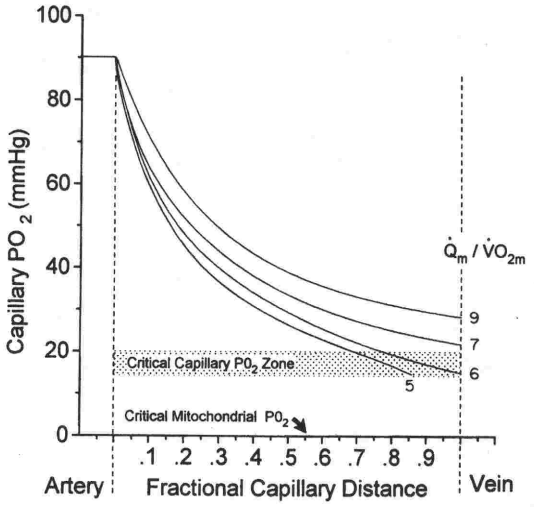

Figure 4 Model of muscle capillary bed oxygen partial pressure (PO_2) as blood travels from artery to vein. The model assumes hemoglobin concentration of 15 g/dL, arterial PO_2 of 90 mm Hg and a linear oxygen consumption along the capillary. The rate of fall in capillary PO_2 depends on the muscle blood flow (Qm)/muscle O_2 consumption ($\dot{V}_{O_2}m$) ratio. The curves include a Bohr effect due to a respiratory carbon dioxide production. The capillary PO_2 is heterogeneous along the capillary bed even with a homogeneous $Qm/\dot{V}_{O_2}m$. The end-capillary PO_2 cannot decrease below the critical capillary PO_2. (From Wasserman, Reference 14)

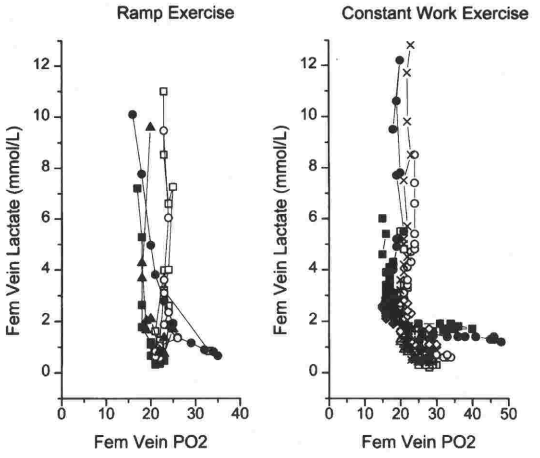

Figure 5 Femoral vein lactate as function of femoral vein PO_2 for increasing (ramp) exercise in five normal subjects (left panel) and 10 constant work-rate exercise tests (five below and five above the LAT) in five additional normal subjects (right panel). The highest femoral vein PO_2 values are where exercise starts. Different symbols represent different subjects. (From Stringer et al, Reference16).

output increase in response to exercise is greater than normal for the metabolic work performed, possibly secondary to the reduced ability to extract O_2.

Changes in mitochondrial density and aerobic enzymes and $\dot{V}_{O_2}$in Heart Failure :

Drexler et al.[5] studied the mitochondrial volume in the muscle of heart failure patients and found that it was decreased in proportion to the reduction in peak $\dot{V}_{CO_2}$. Both Sullivan et al[8] and Massie et al[6] found that the tricarboxylic acid cycle enzyme, succinic dehydrogenase was reduced in the muscle of chronic heart failure patients. These changes, if primary, should result in a reduced ability to extract and therefore consume O_2 during exercise, as described by Haller et al.[19] for defective electron transport chain function.

Changes in fiber type in patients with Chronic Heart Failure :

Massie et al[6], found a decrease percent of type 1 (high oxidative) muscle fibers and increase in percent of type 2ab (low oxidative, high glycolytic muscle fibers) in heart failure patients. Mancini et al[10] found an increase in proportion of type 2b fibers in the skeletal muscle of heart failure patients, although the reductions in the high oxidative fibers (type 1 and type 2a) were not significant.

Changes in Capillary/muscle fiber surface area ratio :

The ratio of capillary to muscle fiber area was investigated by Mancini et al.[10], Massie et al.[6]and Sullivan et al.[8]. These investigations could not detect a significant difference in the capillarization of the leg skeletal muscle of heart failure patients as compared to normal. It should be recognized that the biopsies are taken at rest. Therefore the capillary/fiber area ratio does not reflect the differences in the hyperemia that may develop in the patient with chronic heart failure and the normal subject.

Wilson et al.[7] described two populations of heart failure patients, those with reduced leg blood flow and those with normal leg blood flow during leg exercise. It should be noted that the critical measurement to

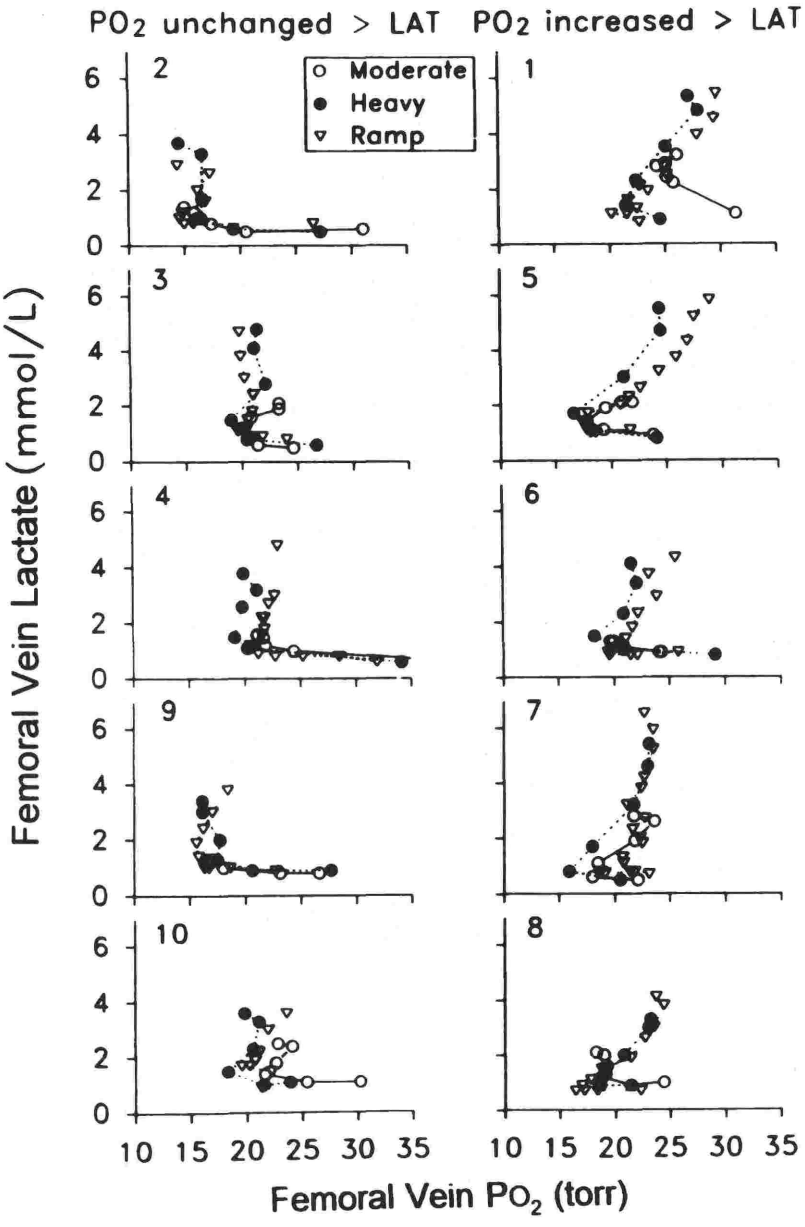

Figure 6 Femoral vein lactate as a function of oxygen partial pressure (PO_2) during two constant work rate tests of moderate and heavy work intensity and an incremental (ramp) exercise test for 10 patients with chronic heart failure. Numbers in panel correspond to the subject number in the original report. The highest PO_2 values were at the start of exercise. Femoral vein lactate increased after femoral vein PO_2 reached its lowest value. After reaching the minimum value, PO_2 was unchanged in five (left column) and increased in five (right column) patients. (From Koike et al, Reference 20).

make is O_2 flow relative to O_2 requirement (see Fig. 4), not blood flow. Thus patients with anemia or increased carboxyhemoglobin can have a normal blood flow but reduced O_2 flow to the exercising muscle.

Lactate increases at a low $\dot{V}O_2$ in Heart Failure:

The critical capillary PO_2 in normal and heart failure patients. Stringer et al.[16] described that lactate increased at submaximal exercise after the lowest PO_2 was reached in the end-capillary blood and referred to this as the critical capillary PO_2. Koike et al.[20] found that heart failure patients also reached a minimal capillary PO_2 at submaximal exercise and above which lactate started to increase (Fig. 6). He referred to this as the critical capillary PO_2 in his heart failure patients. When comparing the critical capillary PO_2 values of Stringer et al[16] and Koike et al[20], the critical capillary PO_2 values were similar but slightly less in the chronic HF patients compared to the same measurements in fit normal subjects (Fig. 7)[21].

Because it has been shown that lactate increases in blood coming from the exercising muscle after the lowest capillary PO_2 is reached[16,20], and lactate increases at a lower $\dot{V}O_2$ the worse the heart failure[4], if the peripheral mechanisms were the primary limitation, the increase in lactate would be expected to take place at a higher PO_2, the worse the exercise tolerance. Koike et al[20], as shown by Wasserman[21] found that the opposite was the case; the worse the exercise tolerance, the lower was the critical capillary PO_2 (Fig 7). Yamabe et al[22], studying a much larger patient population than Koike et al.[20], also found a lower femoral vein PO_2 the lower the peak $\dot{V}O_2$ during maximal leg exercise in heart failure patients. These findings are the opposite of what might be expected if the peripheral changes were primary, i.e., the critical capillary PO_2 would be expected to be higher, the more severe the skeletal muscle defect in the heart failure patient. The finding that the critical capillary PO_2 is able to decrease to values as low as that in normal subjects, or lower, in contrast to that which must be postulated and has been experimentally found when a defect in bioenergetic enzyme function takes place[17~19], provides a very strong argument against the primacy of the peripheral mechanism limiting the exercise performance of chronic heart failure patients.

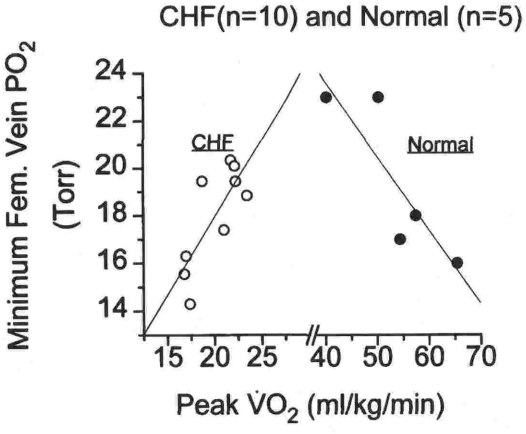

Figure 7 Lowest femoral vein PO_2 (critical capillary PO_2) versus peak $\dot{V}O_2$ in patients with chronic heart failure (CHF) and fit normal subjects. Linear regression lines were separately calculated for each group. For patients, the r=0.70 (P=0.01). For normal subjects, r=0.86 (P=0.06). Data taken from references 16 and 20, and figure reproduced from reference 21.

Discussion

To address the question as to the relative importance of peripheral versus central factors limiting exercise in chronic heart failure, examination of the critical capillary PO_2 with respect to that of normal subjects and as related to the magnitude of dysfunction, is probably the most relevant parameter to address. Any peripheral mechanism, if primary, should reduce the ability to utilize O_2. The finding that the critical capillary PO_2 is as low as that achieved by normal subjects (Fig. 7) argues against peripheral factors being the primary mechanism in the exercise limitation of chronic heart failure patients. An additional argument against peripheral factors being the primary mechanism is that the critical capillary PO_2 is directly related to the peak $\dot{V}O_2$. If the peripheral mechanisms accounted for the exercise limitation, the critical capillary PO_2 should increase as the peak $\dot{V}O_2$ de-

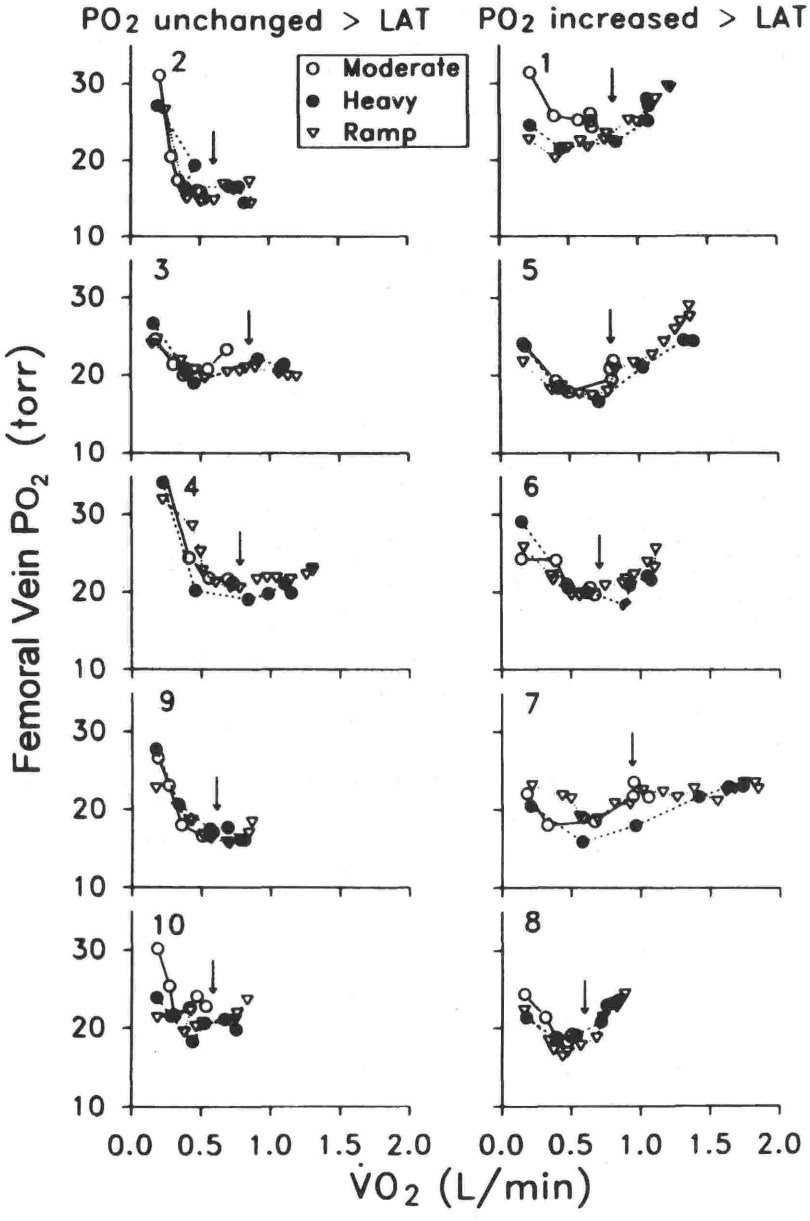

Figure 8 Femoral vein oxygen partial pressure (PO_2) plotted as a function of oxygen uptake ($\dot{V}_{O_2}$) during two constant work rate tests of moderate and heavy work intensity and an incremental (ramp) exercise test for 10 patients with chronic heart failure. Numbers in panel correspond to the subject number in the original report. Femoral vein PO_2 rapidly decreased toward a minimal value with increasing $\dot{V}_{O_2}$. After the femoral vein PO_2 reached its nadir, it increased in five patients despite increasing V_{O_2}(right column), but was unchanged for the other five patients (left column). Arrows show the lactic acidosis threshold determined non-invasively by the v-slope method (23) during the incremental exercise test (from Koike et al, Reference 20).

creased, as shown for the fit normal subjects which we studied (Fig. 7).

The small but significant changes in muscle fiber type distribution found might be secondary to the relative inactivity of the patient imposed by the disease

state. Whether the muscle fiber type changes when the patient undergoes an exercise rehabilitation program apparently has not been studied.

Review of the right column of figure 8, in which the results of 5 patients are displayed, shows that the P_{O_2} increases as the exercise work rate is increased. It might be argued that as work rate is increased toward peak exercise, peripheral mechanisms become of increasing importance in these patients. However, Yamabe et al.[22] measured femoral vein P_{O_2} in his patients at peak exercise and found a direct rather than inverse relationship between P_{O_2} at peak exercise and peak $\dot{V}_{O_2}$. This is opposite to what would be expected if the peripheral factor were primary. The increasing P_{O_2} with work rate found by Koike et al.[20] is possibly due to inhomogeneous muscle blood flow/metabolic rate ratios ($\dot{Q}m/\dot{V}_{O_2}$ m). In the presence of inhomogeneity, as work rate increased, the low $\dot{Q}m/\dot{V}_{O_2}m$ muscle units would have less influence on the mixed femoral vein P_{O_2} than the high $\dot{Q}m/\dot{V}_{O_2}m$ muscle units and the P_{O2} at the femoral vein should increase (move to a higher ratio $\dot{Q}m/\dot{V}_{O_2}m$ curve as shown in figure 4).

In summary, while $\dot{V}_{O_2}$ relative to work rate is normal at very low work rates, the increase in $\dot{V}_{O_2}$ is less than expected as work rate increases. The discrepancy between normal and heart failure patients in exercise $\dot{V}_{O_2}$ is more marked at a given maximal work rate for the heart failure patient. This reduction in $\dot{V}_{O_2}$ is associated with a greater lactic acidosis at the work rate performed. The observation that the critical capillary P_{O_2} is as low as normal and is lower for the greater exercise limitation, is direct evidence that peripheral factors are not primary in the exercise limitation of heart failure patients.

Conclusions

1. Heart failure patients extract O_2 normally during exercise.
2. Failure for $\dot{V}_{O_2}$ to increase normally in chronic HF reflects slow regeneration of ATP, aerobically. Thus the rapidly exhaustible anaerobic mechanisms (phosphocreatine hydrolysis and pyruvate to lactate mechanisms) are used to regenerate ATP, leading to early lactic acidosis and muscle fatigue.
3. Changes in muscle are not primary mechanisms limiting exercise in heart failure. If they were, muscle O_2 extraction should be decreased.
4. Inadequate O_2 transport, not inadequate O_2 utilization by muscle, is the cause of exercise limitation in chronic HF.

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