Metabolic Assessment of Exercise in Chronic Heart Failure Patients Treated with Short-term Vasodilators

STANLEY A. RUBIN, M.D., KANU CHATTERJEE, M.D., AND WILLIAM W. PARMLEY, M.D.

SUMMARY Short-term vasodilators increase exercise cardiac output without an increase in exercise tolerance when administered to chronic heart failure patients. This study was designed to examine cardiac output, oxygen consumption, and lactate metabolism during exercise in chronic heart failure. Thirteen patients participated in 17 studies during control exercise (C) and during vasodilator exercise after short-term treatment with either hydralazine (H) or prazosin (P). Cardiac output increased during exercise both with hydralazine (C = 5.8 ± 2.3 l/min, H = 6.9 ± 2.3 l/min; p < 0.001) and with prazosin (C = 5.9 ± 2.3 l/min, P = 7.6 ± 2.7 l/min; p < 0.005). Oxygen consumption did not change during exercise either with hydralazine (C = 663 ± 249 ml/min, H = 651 ± 200 ml/min; p > 0.10) or with prazosin (C = 696 ± 246 ml/min, P = 734 ± 245 ml/min; p > 0.10). Peak blood lactate did not change either with hydralazine (C = 49.7 ± 24.2 mg/dl, H = 44.0 ± 21.4 mg/dl; p > 0.05) or with prazosin (C = 33.8 ± 16.5 mg/dl, P = 32.1 ± 12.2 mg/dl; p > 0.10). Vasodilators did not change the rate of lactate disappearance during recovery from exercise. We conclude that short-term administration of vasodilators increased cardiac output during exercise but did not improve nutritional flow to exercising muscle. However, chronic administration of vasodilators with sustained improvement in cardiac output may allow the readjustment of peripheral mechanisms that control the nutritional flow of muscle in order to take advantage of improved cardiac performance caused by vasodilators.

IN PREVIOUS REPORTS on the exercise hemodynamics and exercise capacity of chronic heart failure patients administered short-term oral vasodilators,1,2 we noted that hydralazine and prazosin increased cardiac output during exercise, but did not increase exercise tolerance. It seemed paradoxical to us that improvement of a fundamental abnormality of chronic heart failure — low cardiac output — should not result in improvement of exercise tolerance. Data concerning changes in oxygen consumption and muscle metabolism should clarify these disparate effects of short-term vasodilators. In this study we examined changes in the metabolism of oxygen and lactate during exercise and during recovery from exercise as affected by short-term oral vasodilators.

Variables Measured and Calculated

Intracardiac pressures were measured from a Swan-Ganz triple-lumen catheter that had been inserted into the pulmonary artery. Cardiac output was measured in triplicate from the same catheter by the thermodilution technique. Each thermodilution curve was recorded and inspected for technical accuracy while the cardiac output was calculated by a thermodilution computer. Arterial pressure was measured from a short, indwelling radial artery catheter. Mean pressures were obtained by electronic damping. The calculations for the hemodynamic variables, systemic vascular resistance, stroke volume index and stroke work index were performed using standard formulas.

Arterial and mixed venous blood samples were measured for Po2, PCO2 and pH (Corning Gas Analyzer, Medfield, Massachusetts). Special care was taken to ensure collection of a mixed venous sample not contaminated by pulmonary capillary blood. Oxygen saturation was calculated from standard relations.4 Oxygen content was calculated by multiplication of saturation with blood oxygen carrying capacity (hemoglobin concentration × 1.34). We have compared this calculation of oxygen content to that

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obtained directly by the carbon monoxide method, and found close agreement (5% variation). Oxygen consumption was calculated as the product of cardiac output and arteriovenous oxygen difference.

Mix venous lactate was measured by the enzymatic-spectrofluorometric technique. Lactate concentration from this sampling site should be the same as that from an arterial sampling site, but will vary considerably from a limb venous sampling site. Lactate was measured as duplicate samples at rest, at exercise and during recovery. These data were used to determine peak lactate and rate of lactate disappearance during recovery. In a pilot study, we obtained lactate samples every minute for 15 minutes during recovery from exercise. We found that peak lactate always occurred during the first minute of recovery from exercise. We also found that the rate of lactate disappearance was monoexponential. A time constant could be calculated as the inverse of the power of the exponent, which was determined from curve fitting using standard regression formulas. This time constant is a measure of the initial rate at which lactate decreases in the blood. We subsequently found that a limited sampling regimen of blood samples obtained at 1, 4, 7, 10 and 15 minutes during recovery could duplicate the results of the more extensive sampling technique. This limited sampling regimen was adopted for this study (fig. 1).

Exercise Protocol

Patients exercised during a control period and after vasodilators had increased cardiac output. They exercised in the postabsorptive state at the same time of day for each of the two exercises. Exercise was performed supine in progressive work load stages on a table-mounted leg ergometer. The initial work load was 50 kpm/min and the work load was increased by 50 kpm in 3-minute stages. Patients maintained a constant pedaling rate of 40 rpm. Measurements were taken at maximum symptom-limited exercise, defined by the patients as intolerable symptoms of generalized fatigue, leg fatigue and dyspnea. Patients were only included in this study if they achieved the same peak exercise while on vasodilator drug as at control and if total pedaling duration was within 30 seconds on vasodilator drug as at control. One patient initially entered into this study was excluded from data analysis because the two exercises were not equal. In this group of patients, peak exercise work load varied from 100 kpm/min to 300 kpm/min, while total pedaling duration varied from 6–18 minutes.

Drug Protocol

After control exercise, vasodilator therapy was begun. Five patients received hydralazine only and four received prazosin only. Four patients received both drugs in sequence: Two received hydralazine first and two received prazosin first. The washout period between the two drugs was a median of 36 hours (range 24–48 hours). The drugs were administered every 6 hours for 36–48 hours in incremental doses to a plateau, based on our experience of doses expected to increase exercise cardiac output. The plateau dose for hydralazine was 75 mg every 6 hours in each patient; for prazosin it varied between 5–10 mg every 6 hours between patients. Patients were reexercised 2 hours after the final dose of vasodilator.

Statistical Analysis

Paired analysis between control and vasodilator for each variable was performed by the paired t test.

Results

Cardiac Output (fig. 2)

In the hydralazine group, cardiac output during control exercise was 5.8 ± 2.3 l/min (mean ± sd). During hydralazine exercise increased to 6.9 ± 2.3 l/min (p < 0.001). In the prazosin group, cardiac output during control exercise was 5.9 ± 2.3 l/min. During prazosin exercise increased to 7.6 ± 2.7 l/min (p < 0.005). Cardiac output increased during vasodilator exercise compared with control exercise because stroke volume increased, while heart rate remained unchanged. Combining both vasodilator-treated groups, cardiac output increased during exercise compared with control.

Oxygen Consumption (fig. 3)

In the hydralazine group, oxygen consumption during control exercise was 663 ± 249 ml/min and during hydralazine exercise was 651 ± 200 ml/min (p > 0.10). Four patients showed an increase in oxygen consumption, four showed a decrease, and one showed no change. In the prazosin group, oxygen con-
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FIGURE 2. Effect of vasodilators on cardiac output during exercise. Comparison of hydralazine (H) and prazosin (P) compared to control (C). Patients had a uniform increase in cardiac output, except for one patient, from vasodilators.

FIGURE 3. Effect of vasodilators on oxygen consumption during exercise. Patients had a nonuniform response with small increases or decreases in oxygen consumption from vasodilators. NS = nonsignificant.

FIGURE 4. Effect of vasodilators on peak lactate of exercise. Patients had a nonuniform response with small increases or decreases in lactate from vasodilators.

Peak Lactate (fig. 4)

In the hydralazine group, peak lactate during control recovery was $49.7 \pm 24.2$ mg/dl; during hydralazine recovery it was $44.0 \pm 21.4$ mg/dl ($0.10 > p > 0.05$). Seven patients showed a decrease in lactate and two patients showed an increase. In the prazosin group, peak lactate during control recovery was $33.8 \pm 16.5$ mg/dl and during prazosin recovery was $32.1 \pm 12.2$ mg/dl ($p > 0.10$). Four patients showed a decrease in lactate and four an increase. Combining both vasodilator-treated groups, peak lactate did not change compared with control.

Disappearance Rate of Lactate (fig. 5)

In the hydralazine group, the time constant of lactate disappearance during control was $31.1 \pm 16.7$ minutes and the time constant during hydralazine was $29.8 \pm 13.5$ minutes ($p > 0.10$). Four patients showed...
a decrease in time constant, two patients showed an increase and two showed no change. In the prazosin group, the time constant of lactate disappearance during control was 26.1 ± 7.8 minutes and the time constant during prazosin was 38.9 ± 23.2 minutes ($p > 0.10$). Two patients showed a decrease in time constant, five showed an increase and one patient showed no change. Combining both vasodilator-treated groups, the time constant of lactate disappearance did not change compared with control.

**Hemodynamic Variables During Exercise (table 1)**

Both hydralazine and prazosin significantly increased stroke volume index and stroke work index. Hydralazine did not change wedge pressure, while prazosin significantly decreased it. Therefore, both drugs increased ventricular function during exercise. Neither hydralazine nor prazosin changed heart rate, arterial pressure, or right atrial pressure. Prazosin significantly decreased pulmonary artery pressure; hydralazine did not.

**Discussion**

A number of reports have documented that vasodilators cause an increase in cardiac output during exercise in chronic heart failure. Therefore, a key question as to the usefulness of vasodilator treatment of chronic heart failure is how cardiovascular transport changes. Transport should be considered in terms of tissue blood flow and of tissue uptake, utilization and removal of metabolites. Some data are available on tissue blood flow in chronic heart failure patients. At rest, there is less-than-normal blood flow to many tissues. During exercise, there is less-than-normal blood flow to exercising limbs, and it is likely that this decrease applies specifically to the skeletal muscle of the limb. Some data are also available on oxygen consumption and lactate in chronic heart failure patients. At rest there is a normal oxygen consumption and normal blood lactate. During exercise there is a less-than-normal oxygen consumption and a higher-than-normal blood lactate. Our data, collected without normal patient controls, show that chronic heart failure patients have a high blood lactate at low work loads. These data suggest that heart failure patients have not only a decreased maximum oxygen consumption but also an accumulating anaerobic debt at submaximum work loads.

Short-term vasodilators increased cardiac output during exercise, but did not change oxygen consumption or blood lactate. Similar findings have been reported in several studies in which cardioactive drugs were administered to heart failure patients on a short-term basis. For example, phentolamine increased cardiac output but did not change oxygen consumption during bicycle or forearm exercise. Also, prazosin increased cardiac output but did not change oxygen consumption during bicycle exercise. Similar results have been reported with nitroglycerin ointment, a combination of nitrate-hydralazine, and the inotropic agent salbutamol. In a group of valvular heart disease patients, nitroglycerin slightly increased exercise oxygen consumption. Our data help to explain why short-term drug studies of chronic heart failure may show an increase in cardiac output without an increase in exercise tolerance; but they do not reveal why an acute increase in the cardiac output of heart failure patients does not change oxygen consumption or lactate metabolism. We speculate that there are two classes of physiologic mechanisms to account for this disparity.

First, there may be maldistribution of the increase in cardiac output caused by short-term vasodilators. If this increase were distributed to nonexercising tissues, then exercising skeletal muscle would not benefit from the increase in total flow. Only limited regional measurements of flow in heart failure patients during exercise have been made. It is often believed that metabolic needs are the principal control of organ blood flow during exercise. Vasodilators such as $\alpha$ blockers or direct smooth-muscle agents may not affect the metabolically determined blood flow in exercising skeletal muscle, but instead, blood flow in-

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Values are mean ± SD.

Abbreviations: HR = heart rate; MAP = mean arterial pressure; MPA = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; MRA = mean right atrial pressure; CO = cardiac output; AV-O₂ = arteriovenous oxygen difference; VO₂ = oxygen consumption; Lp = peak lactate during recovery; Lr = time constant of lactate disappearance during recovery; SVR = systemic vascular resistance; SVI = stroke volume index; SWI = stroke work index; NS = not significant.
creases in nonexercising tissues. An increase in blood flow to nonexercising tissues could be beneficial in preserving organ function or in regulating non-nutritional aspects of exercise, such as heat dissipation through skin blood flow. Our simple measurements of cardiac output and arteriovenous oxygen difference cannot confirm this mechanism.

Second, cardiovascular transport may be foiled because of abnormal distribution or utilization of flow within tissues.18 If blood flow is shunted at precapillary sphincters, it won't be delivered downstream. If multiple capillary beds remain closed, then there will be a maldistribution of blood flow. If the walls of exchange vessels are thickened by edema, then decreased lumen size will result in decreased capillary transit time and impairment of capillary exchange. Or, this edema may directly impair the capillary filtration coefficient. If mitochondria and respiratory enzyme systems have been decreased by chronic physical deconditioning, then delivered oxygen will not be utilized. Our observations are compatible with this class of mechanisms, but do not distinguish among them.

Another issue is the effect of vasodilators on recovery from exercise. After exercise, rest represents a cessation of activity as well as a period of recovery and repair from exercise. During this time, the accumulated metabolic debts of exercise are repaid. The rapidity of this recovery process is a marker of the body's ability to prepare for the next exercise. Extensive investigations of lactate metabolism in healthy people show that during fatigueing exercise, muscle accumulates a high concentration of lactate and that, only during early recovery, muscle releases a small portion of this lactate into the blood.19 Our analysis of lactate during recovery in heart failure patients shows that blood levels decrease in a monoexponential decay. These data are compatible with studies of the flux of muscle lactate and are congruent with a single compartment model of blood lactate in which no further lactate enters the blood after exercise and lactate is removed at a constant fraction per unit time. The principal organ of lactate removal is the liver, but also contributing to removal are heart and kidney. Our data show that vasodilators do not change this disappearance rate and suggest that either liver blood flow or liver gluconeogenesis rate is unchanged.

Different effects of vasodilators on exercise might be observed during long-term administration. Our observations on exercise are compatible with severe chronic physical deconditioning and resultant alterations in peripheral tissues.20 If vasodilators chronically increase cardiac output and cardiac performance, improvement in physical conditioning might result. Changes in the peripheral circulation and tissues might result in an improved cardiovascular transport caused by an increase in oxygen consumption and a decrease in lactate. Studies on exercise tolerance of heart failure patients treated chronically by vasodilators have shown an increase in work load performance.21-22 However, these studies have not included data on cardiac output or oxygen consumption. A recent report on the effects of chronic nitrate administration suggests that oxygen consumption and exercise tolerance improved without a change in cardiac output.24

In summary, our study shows that short-term administration of vasodilators does not improve the abnormal peripheral metabolic processes of heart failure patients during exercise or during recovery from exercise. This study also raises exciting possibilities for the study of abnormal cardiovascular transport functions in heart failure.

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References


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