Acute Substantial Benefit of Inotropic Therapy with Amrinone on Exercise Hemodynamics and Metabolism in Severe Congestive Heart Failure

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SUMMARY The acute hemodynamic and metabolic effects of amrinone during exercise were studied in eight patients with severe congestive heart failure. The patients exercised to exhaustion on an upright bicycle ergometer at a fixed work load of 25 W. During the control period of exercise, exhaustion occurred at 3.16 ± 1.39 minutes. Stroke volume increased from 29.5 ± 5.8 to 38.7 ± 9.5 ml (p < 0.01), arteriovenous oxygen difference from 7.6 ± 1.3 to 9.6 ± 0.6 ml/100 ml (p < 0.001), oxygen consumption from 231 ± 38 to 468 ± 111 ml/min (p < 0.001) and arterial lactate concentration from 1.07 ± 0.25 to 5.02 ± 1.45 mmol/l (p < 0.01). During exercise after administration of amrinone, exhaustion occurred significantly later than during the control period: 6.28 ± 2.07 vs 3.16 ± 1.39 minutes (p < 0.05). At a time equal to the point of exhaustion during the control period, stroke volume was significantly greater after amrinone (46.7 ± 9.8 vs 38.7 ± 9.5 ml, p < 0.05), arteriovenous oxygen difference and arterial lactate concentration were significantly lower (7.7 ± 0.9 vs 9.6 ± 0.6 ml/100 ml [p < 0.05] and 2.96 ± 1.01 vs 5.02 ± 1.45 mmol/l [p < 0.05], respectively) and oxygen consumption was similar.

At the point of exhaustion during exercise after amrinone, there were further increases in stroke volume (to 54.0 ± 11.6 ml, p < 0.05), and oxygen consumption (to 674 ± 141 ml/min, p < 0.05), while arteriovenous oxygen difference and arterial lactate concentration reached values similar to those during control exercise. Thus, amrinone increased exercise capacity, improved exercise hemodynamics, and probably decreased anaerobic metabolism at a given duration of exercise.

AMRINONE is a new synthetic cardiotonic agent that does not act through the mechanisms thought to mediate the action of digitalis glycosides or catecholamines.1 Amrinone has been shown to improve left ventricular performance at rest in patients with severe congestive heart failure. This improvement occurs after either i.v.2-4 or oral administration of amrinone and is characterized by an increase in cardiac output (CO) and a reduction in left ventricular filling pressure without changes in mean arterial pressure (MAP) or heart rate (HR). Although preliminary data suggest that long-term therapy with amrinone can increase the exercise capacity of patients with severe chronic heart failure,5-9 the hemodynamic and metabolic responses to exercise after acute administration of the drug have not been evaluated.

The major hemodynamic aims in the therapy of congestive heart failure are to control pulmonary and peripheral congestion and to improve exercise performance. Potent diuretics have helped to control the former problem, but do not acutely improve exercise performance. Short-term administration of vasodilators to patients with severe heart failure improves both resting and exercise hemodynamics, but does not increase exercise capacity.8-10

Accordingly, the effects of i.v. amrinone on the hemodynamic and metabolic response to upright exercise were evaluated in eight patients with refractory congestive heart failure.

Methods

Patients

Seven men and one woman with chronic congestive heart failure refractory to digitalis, diuretics and nitrates were studied. The average age of the patients was 46 years (range 17–58 years). Three had ischemic heart disease documented by past myocardial infarction or coronary arteriograms. Three others had a cardiomyopathy of unknown etiology. The remaining two patients had remained in congestive heart failure after successful aortic valve replacement. The absence of significant mitral regurgitation was documented by left ventriculography in six patients. All were severely restricted in their activity: five patients were in New York Heart Association functional class IV and three were in class III. Sinus rhythm was present in all patients except one, who was in atrial fibrillation. Left ventricular ejection fraction, determined by the gated technique using technetium-99m pertechnetate, averaged 20% for the eight patients (range 17–33%). Nitrates were discontinued 2 days before the study. Patients were maintained on their regular doses of digoxin and furosemide. The nature, potential benefits and possible risks of the study were fully explained to the patients, who then gave written informed consent. The protocol was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine. All patients were studied in the coronary care unit.

Hemodynamics

One day before the study, patients underwent right-heart catheterization using a #7F flow-directed, balloon-type thermodilution catheter (Gould Laboratories). On the day of the study, an intra-arterial in-
dwellling catheter was inserted percutaneously into a radial artery for measurement of systemic arterial pressure (SAP) and for withdrawal of blood samples. SAP and right atrial (RAP), pulmonary arterial (PAP) and pulmonary capillary wedge (PCWP) pressures were determined using Gould Statham P231D transducers and recorded on an Electronics for Medicine VR6 recorder. HR was recorded continuously from a bedside ECG. CO was performed by thermodilution using iced 5% dextrose in water. Measurements were made in triplicate with a less than 10% variation. CO was computed by a bedside computer (model SP 1425 Gould Laboratories) and confirmed periodically by appropriate integration of recorded curves. Resting hemodynamics were measured with the patient sitting upright on the bicycle ergometer. The pressure transducers were positioned at the level of the fourth intercostal space for determination of RAP, PAP and PCWP and at the level of the handlebars for SAP. Two sets of similar resting determinations were obtained 15 minutes apart. During control exercise, PAP, mean RAP and mean SAP were monitored and CO was continually measured. PCW was measured after exercise. After 3-4 hours of rest, amrinone was administered intravenously and the exercise protocol was repeated. Hemodynamic measurements were performed as before. During exercise after amrinone, special attention was taken to measure PCWP at the same time at which exhaustion was reached during control exercise. Derived hemodynamic variables, stroke volume (SV) and systemic vascular resistance (SVR) were calculated from standard formulas.

Oxygen Saturations and Arterial Lactates

Oxygen saturations were determined with an oximeter (American Optical) and low mixed venous saturations were verified by blood gas analysis. During control exercise, oxygen saturations of systemic arterial and pulmonary arterial (PA) blood were measured at rest and after exercise. During exercise while receiving amrinone, an additional measurement of systemic arterial and PA saturations were obtained at times equivalent to exhaustion during control exercise. The arteriovenous oxygen difference (A-V O₂) was calculated as arterial saturation (fraction) - PA saturation (fraction) 1.34 x hemoglobin concentration. Oxygen consumption (VO₂) in ml/min was calculated as the product of CO and A-V O₂. Arterial lactate concentration was measured by the enzymatic-spectrofluorometric technique and expressed in mmol/l. Blood for lactate measurements and oxygen saturations was drawn at the same time. At rest and during exercise, lactate levels were measured in duplicate. Two samples were taken at the end of exercise and averaged. Even without averaging, the two samples were not significantly different.

Exercise Protocol

Exercise testing was performed with the patient upright on a bicycle ergometer (Warren E. Collins, Inc.) with his feet secured to the pedal. Two exercise tests were performed within 72 hours of control exercise to determine reproducibility and to familiarize the patient with the apparatus. Patients were tested at the same time of the day and in the postabsorptive state at least 4 hours after their dose of furosemide. After a short warm-up period, the patients performed control exercise at a fixed work load of 25 W and pedaled at a frequency greater than 35 rpm. All patients exercised until exhaustion, when they complained of severe leg discomfort and profound fatigue. In no instance did shortness of breath or angina limit the duration of exercise. After receiving amrinone, patients exercised in similar fashion at a fixed work load of 25 W until exhausted.

Amrinone Protocol

After control exercise, the patients returned to bed and rested for 3-4 hours. After supine baseline hemodynamic determinations were obtained, i.v. amrinone (supplied by Sterling-Winthrop Research Institute) was administered by continuous infusion at a rate of 40 μg/kg/min. Sixty minutes later, once CO in the supine position had increased to an average of 48% over baseline (range 24-72%), patients were positioned on the bicycle ergometer. Hemodynamic and metabolic variables were measured at rest; the patients then exercised until exhaustion while amrinone was continuously infused.

Statistical Analysis

Exercise responses in the control state and during amrinone administration were compared at a time corresponding to the time of exhaustion during the control period. Hemodynamic determinations were examined using a mixed-model analysis of variance. Each patient was assessed at rest and exercise, with and without administration of amrinone. Thus, data under four conditions were obtained for each patient. The mean effects of exercise and of amrinone were evaluated in the absence of any treatment by exercise interactions.

The effects of amrinone were subsequently analyzed using a single-factor, repeated-measures analysis of variance. After administration of amrinone, each patient was examined at rest, at a time equivalent to exhaustion during control exercise, and at exhaustion. Comparisons were made between the mean values for each hemodynamic determination at the three times using Duncan's multiple-range test. The results are expressed as mean ± SD.

Results

Hemodynamic responses to exercise in the control state and during amrinone administration are given in tables 1 and 2. The mean duration of control exercise until exhaustion was 3.16 ± 1.39 minutes for eight patients (fig. 1). SV increased from 29.5 ± 5.8 to 38.7 ± 9.5 ml (p < 0.01) and PCWP increased from 26.1 ± 5.2 to 34.7 ± 4.8 mm Hg (p < 0.001) (fig. 2). MAP and RAP increased significantly and SVR declined (table 1). The A-V O₂ increased from 7.6 ± 1.3 to 9.6
Hemodynamic Determinations During Control Exercise

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± 0.6 ml/100 ml (p < 0.001) and VO₂ increased from 231 ± 39 to 468 ± 111 ml/min (p < 0.001) (fig. 3). Arterial lactate concentration, determined in four patients (table 3), increased from 1.07 ± 0.25 to 5.02 ± 1.45 mmol/l (p < 0.01) (fig. 4).

The duration of exercise until exhaustion was significantly greater during administration of amrinone than during the control period (6.28 ± 2.07 vs 3.16 ± 1.39 minutes, p < 0.05). At a time equal to that which produced exhaustion in the control period, SV had increased from a resting value of 40.8 ± 6.9 ml to 46.7 ± 9.8 ml (p < 0.05), while PCWP had increased from 21.7 ± 3.9 to 33.1 ± 5.4 mm Hg (p < 0.001) (fig. 2). Thus, at rest, the patients who received amrinone had a significantly higher SV and a lower PCWP (p < 0.01). At the same duration of exercise, the patients who received amrinone developed a significantly higher SV than during control exercise (p < 0.05), but PCWP and HR were similar. While receiving amrinone, patients developed significantly higher MAP and RAP and lower in SVR compared with resting values (table 2). At rest, MAP was not changed by amrinone, and RAP was significantly reduced, from 8.1 ± 3.5 to 4.1 ± 2.8 mm Hg (p < 0.001). At the same duration of exercise, both of these pressures were significantly lower after amrinone than during the control period: 85.1 ± 11.0 vs 88.1 ± 14.6 mm Hg (p < 0.05) and 9.2 ± 3.7 vs 13.1 ± 2.6 mm Hg (p < 0.001), respectively. In the patients treated with amrinone, SVR was lower both at rest (1465 ± 268 vs 1911 ± 495 dyn-sec-cm⁻⁵) (p < 0.001) and at the same duration of exercise (1056 ± 213 vs 1327 ± 566 dyn-sec-cm⁻⁵) (p < 0.001).

During amrinone administration, the resting A-V

![Figure 1. Oxygen consumption related to duration of exercise. At rest, oxygen consumption is similar in the control period (CR) and on amrinone (A). After 3.16 minutes of exercise, exhaustion is reached in patients on no therapy (CEX) while at equal duration of exercise, the oxygen consumption is the same for patients on amrinone (AE). Exhaustion after amrinone (AE) is only reached at 6.28 minutes, and then only at a much higher level of oxygen consumption. *p < 0.05; ***p < 0.001.](http://circ.ahajournals.org/doi/10.1161/01.CIR.64.5.968)
Table 1. (Continued)

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± 5.2 ± 4.8 ± 3.5 ± 2.6 ± 495 ± 566 ± 1.3 ± 0.6 ± 38 ± 111 ± 1.39

< 0.001 < 0.001 < 0.001 < 0.001 < 0.001

Figure 2. Relation between stroke volume and pulmonary capillary wedge pressure during control exercise and during exercise after amrinone. CR = control at rest; AR = rest after amrinone; AE = exercise after amrinone at a time equal to exhaustion during the control state; CEx = control exercise to exhaustion; AEx = exercise to exhaustion after amrinone. *p < 0.05; **p < 0.01.

Figure 3. (top) Relation between oxygen consumption and exercise duration. (middle) Cardiac output related to oxygen consumption. (bottom) Arteriovenous oxygen difference as a function of oxygen consumption. Abbreviations as in figure 2. *p < 0.05; **p < 0.01; ***p < 0.001.
TABLE 2. Hemodynamic Determinations During Exercise After Amrinone

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*p (AE vs AR) < 0.001
*p (AEx vs AE) < 0.05
*NS

Abbreviations: HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVR = systemic vascular resistance; A-V O₂ = arteriovenous oxygen difference; VO₂ = oxygen consumption; AR = rest after amrinone; AE = exercise on amrinone at a time equal to exhaustion during the control state; AEx = exercise to exhaustion after amrinone.

O₂ decreased from 7.6 ± 1.3 to 5.6 ± 0.7 ml/100 ml (p < 0.001), while VO₂ and lactate concentrations did not change significantly (Table 3). However, at the duration of exercise that produced exhaustion during the control period, the A-V O₂ and the arterial lactate concentration were significantly lower after amrinone: 7.7 ± 0.9 vs 9.6 ± 0.6 ml/100 ml (p < 0.01) and 2.96 ± 0.01 vs 5.02 ± 1.45 mmol/l (p < 0.05), respectively (fig. 4). The VO₂ was similar to that during the control period.

When patients exercised until exhaustion after amrinone, the duration of exercise increased and the hemodynamic and metabolic responses were significantly different. SV increased further, from 46.7 ± 9.8 to 54.0 ± 11.6 ml (p < 0.05), and PCWP increased from 33.1 ± 5.5 to 37.0 ± 5.7 mm Hg (p < 0.05). HR and RAP also increased further, and SVR decreased (table 2). There were also additional significant increases in A-V O₂ (to 9.5 ± 0.5 ml/100 ml), VO₂ (to 674 ± 141 ml/min) and arterial lactate (to 5.13 ± 0.73 mmol/l) (all p < 0.05). Exhaustion occurred at the same A-V O₂ and lactate concentration before and after administration of amrinone.

Discussion

In patients with severe heart failure, administration of amrinone results in substantial hemodynamic and metabolic improvements during submaximal exercise performed to exhaustion. In the control state, the resting CO of these patients was low, while the left ventricular filling pressure, as measured by the PCWP, was elevated. During exercise until exhaustion, CO only increased from 3.10 to 4.93 l/min, while left ventricular filling pressure increased substantially, from 26.1 to 34.7 mm Hg. Exercise in the upright position was always limited by severe fatigue rather than by shortness of breath, despite the very high left ventricular filling pressures. In general, the increase in CO was due to increases in HR and SV. However, the changes in SV during exercise vary in patients with severe left ventricular dysfunction.15,16 The mean SAP increased in all but one patient.

At the point of exhaustion, in the absence of amrinone, VO₂ doubled and was associated with a fivefold increase in arterial lactate levels. The latter would indicate that the patients were performing at close to peak aerobic capacity.18 The maximal A-V O₂ reached by our patients was markedly lower than that reached by normal subjects, i.e., 9.6 vs 15.9 ml/100 ml.18 The moderate anemia observed in our patients may partially explain this disparity. If the hemoglobin levels are corrected to normal levels, i.e., 16 g/100 ml for males and 14 g/100 ml for females, the A-V O₂ at exhaustion would reach about 13 ml/100 ml. This is...
TABLE 2. (Continued)

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±2.8 ±3.7 ±2.7 ±268 ±213 ±246 ±0.7 ±0.9 ±0.5 ±58 ±93 ±141 ±2.07
<0.001 <0.05 <0.001 <0.001 <0.001 <0.05
<0.05 <0.05 <0.05 <0.05

still less than anticipated, and may be attributed to metabolic and ultrastructure changes in peripheral musculature induced by physical inactivity, as previously suggested. ¹⁷, ¹⁸

To study exercise performance in patients with severe heart failure and extremely limited exercise tolerance, important modifications of the exercise protocol were necessary. We found it useful to maintain the same work load and study the time over which this effort could be sustained. Indeed, in patients with severe heart failure, an important limitation to exercise appears to be endurance. In contrast, in the patient with coronary artery disease, in whom evidence of myocardial ischemia is elicited by increasing myocardial oxygen requirements as much as possible, maximal work load, rather than endurance at submaximal load, is sought. ¹⁹ During the control state, all patients exercised at a work load of 25 W, which is equivalent to walking on level ground at 1.2 mph. ²⁰ Nevertheless, this was a great burden and only one patient could maintain such a level of exercise for more than 4 minutes. In view of the very limited duration of exercise in such circumstances, no purpose would have been served by increasing the work load. Exercise at a work load of 25 W corresponds reasonably well to the daily physical activity of these patients and thus has greater clinical implications than the maximal work load.

During exercise until exhaustion in patients receiving amrinone, CO increased to a substantially higher level than during control exercise, and PCWP increased from 21.7 to 37.0 mm Hg. As during the control period, the augmentation in CO was due to increases in HR and SV. The maximal A-V O₂ and the lactate concentration at exhaustion were the same as during the control state, but at the exercise duration that produced exhaustion during control, both values were significantly lower after administration of amrinone. The decrease in arterial lactate concentration probably reflects a reduced amount of anaerobic metabolism in the exercising muscles. Even though this interpretation has been questioned, ²¹ blood lactate concentrations have been shown to correlate well with muscle lactate concentration. ²² Further, although the liver has been thought to be an important organ for the removal of lactate during exercise,²³ this notion has not been confirmed,²⁴, ²⁵ and the role of the liver for elimination of the lactate may be regarded as minimal.²⁶ Thus, administration of amrinone probably lowered arterial lactate concentration by decreasing production in exercising muscles rather than by increasing hepatic extraction. Moreover, at exhaustion, the VO₂ attained after amrinone was further increased, even though the work load remained constant.

In the present study we found that patients with severe heart failure do not attain a steady VO₂ when exercising to exhaustion at a submaximal load. Thus, although a constant load was maintained, oxygen con-

FIGURE 4. Relation between arterial lactate concentration and oxygen consumption. *p < 0.05. Abbreviations as in figure 2.
The salutary effects of amrinone on the determinants of VO\(_2\) stand in sharp contrast to those of vasodilators. Rubin et al.\(^6\) using a graded exercise protocol, studied 16 patients with chronic heart failure and found that hydralazine did not alter maximal VO\(_2\). Although therapy with hydralazine permitted a significantly greater CO to be attained with exercise, it was associated with less widening of the A-V O\(_2\) than during control exercise. For this reason, the maximal VO\(_2\) was not increased. In contrast, after amrinone, our patients could reach an A-V O\(_2\) similar to that attained during control exercise. The fact that we did not use an exercise protocol similar to that of Rubin et al. cannot account for the different effects of amrinone and hydralazine on the A-V O\(_2\). By using a graded exercise protocol, Rubin et al.\(^6\) increased the likelihood of obtaining a maximal widening of the A-V O\(_2\). After amrinone, patients had a higher VO\(_2\) as a result of increases in CO and A-V O\(_2\). At rest, A-V O\(_2\) was lower in patients receiving amrinone, while at exhaustion it reached the same level as observed during the control period of exercise.

Our patients with severe heart failure all complained of profound fatigue and severe leg discomfort when exercised until exhaustion. Exhaustion occurred at the same A-V O\(_2\) and elevated lactate concentration during control exercise and exercise after amrinone. Moreover, exhaustion was associated with a higher ventricular filling pressure during exercise after amrinone. Therefore, it is likely that an inadequate increase in CO and impaired perfusion of exercising muscles, rather than an elevated ventricular filling pressure, limited the exercise capacity in our patients. Amrinone improves cardiac performance and probably reduces anaerobic metabolism at a given level of exercise, allowing patients to exercise longer. By enabling patients with congestive heart failure to exercise with less discomfort, one might expect further improvement in exercise capacity due to a training effect.\(^9, 20\)

References

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Acute Vasodilator Therapy Increases Renal Clearance of Digoxin in Patients with Congestive Heart Failure

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SUMMARY We studied the effect of vasodilator therapy on renal digoxin clearance in patients with chronic congestive heart failure. Intravenous administration of nitroprusside or hydralazine to eight patients with severe heart failure produced the expected increase in cardiac output and a decrease in central circulatory pressure. Renal clearance of sodium para-aminohippurate and estimated renal blood flow increased without a change in glomerular filtration rate. Total renal clearance of digoxin increased by 50% during vasodilator therapy. Thus, acute administration of vasodilator increases renal digoxin clearance without changing glomerular filtration rate, suggesting an increase in tubular secretion of digoxin. Long-term vasodilator therapy may alter the maintenance dosage of digoxin required for optimal treatment of patients in congestive heart failure.

IN PATIENTS with congestive heart failure, renal excretion of digoxin occurs as a result of glomerular filtration and net tubular secretion of unchanged drug. Tubular reabsorption of digoxin may also be important in patients with low urinary flow rates. Patients with congestive heart failure often have substantially reduced renal blood flow (RBF) and may also have a decreased glomerular filtration rate (GFR). We recently showed that acute vasodilator therapy results in improved renal hemodynamics in such patients. Because vasodilator-induced improvements in renal function could influence renal digoxin clearance, we studied the effects of acute vasodilator therapy on the renal handling of digoxin.

Methods

Eight patients with congestive heart failure (New York Heart Association functional class III or IV) underwent hemodynamic and renal clearance studies. The mean age was 54 years. The clinical characteristics and laboratory evaluation of these patients have been presented. Of the nine subjects included in the original study, plasma and urine digoxin concentrations were measured in eight and the results are reported herein. No patient had a serum creatinine level greater than 1.5 mg/dl or a history of allergy to the study drugs. The protocol was approved by the University of California, San Francisco, Committee on Human Research. Each patient gave informed written consent.

All cardiac medications, including digoxin, diuretics and vasodilators, were discontinued 24 hours before the study. In the catheterization laboratory, catheters were placed in a femoral or radial artery and a forearm vein, and a Swan-Ganz thermodilution catheter was inserted into the pulmonary artery. In seven patients a Foley catheter was positioned in the bladder and connected to a gravity drainage apparatus; in the eighth patient urine was collected during spontaneous voiding. An i.v. loading dose of sodium para-aminomhippurate (PAH) (Merck, Sharp & Dohme, Inc.) and iothalamate meglumine (Malinckrodt, Inc.) was followed by constant infusion of these compounds in isotonic dextrose in water at 1 ml/min for renal clearance measurements. Patients remained in bed for the entire study period and were allowed free access to drinking water.

The protocol consisted of four experimental periods. After initial measurement of hemodynamic variables and collection of blood and urine samples (period 1, control 1), sodium nitroprusside (Roche Laboratories) was administered intravenously at a starting dose of 5 µg/min. The infusion rate was gradually increased until repeat thermodilution

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