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Improved Hemodynamic Function and Mechanical Efficiency in Congestive Heart Failure With Sodium Dichloroacetate

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Objectives. The purpose of this study was to determine whether sodium dichloroacetate improves hemodynamic performance and mechanical efficiency in congestive heart failure.

Background. Congestive heart failure is associated with impaired hemodynamic performance and reduced mechanical efficiency. Dichloroacetate stimulates pyruvate dehydrogenase activity by inhibition of pyruvate dehydrogenase kinase, which results in inhibition of free fatty acid metabolism and stimulation of high respiratory quotient glucose and lactate consumption by the heart. Facilitation of glucose and lactate consumption with dichloroacetate should improve mechanical efficiency of the failing ventricle.

Methods. Ten patients with New York Heart Association functional class III to IV congestive heart failure were studied. Dichloroacetate (50 mg/kg body weight) was administered intravenously for 30 min, with measurements of hemodynamic variables, coronary sinus blood flow and blood gas, glucose and lactate levels for 2 h. The same patients were also given dobutamine (5 to 12.5 μg/kg per min) for comparison.

Results. Therapeutic levels of dichloroacetate were achieved (100 to 160 μg/liter of plasma). Myocardial consumption of lactate was stimulated from 29% to 37.4%. Forward stroke volumes increased (+5.3 ml/beat, $p < 0.02$), as did left ventricular stroke work (+1.8 g-m/m^2 per beat, $p < 0.02$) and left ventricular minute work (from 1.38 to 1.55 kg-m/m^2 per min, $p < 0.01$). Myocardial oxygen consumption decreased (from 19.3 to 16.5 ml/min, $p = 0.06$) as left ventricular minute work increased. Left ventricular mechanical efficiency thus improved from 15.2% to 20.6% ($p = 0.03$).

Dobutamine administration resulted in the opposite trend with respect to myocardial lactate extraction (from 34% to 15.3%, $p < 0.02$). Stroke volume increased (+7.4 ml/beat, p = NS vs. dichloroacetate), as did left ventricular minute work (from 1.29 to 1.59 g-m/m^2 per min, $p < 0.01$ vs. dichloroacetate) and myocardial oxygen consumption (from 18.6 to 21.0 ml/min, $p = 0.06$ vs. dichloroacetate). Left ventricular mechanical efficiency did not change with dobutamine administration (from 16.4% to 15.8%, p = NS).

Conclusions. Dichloroacetate administration stimulates myocardial lactate consumption and improves left ventricular mechanical efficiency. Forward stroke volume and left ventricular minute work increase significantly, with a simultaneous reduction in myocardial oxygen consumption. Dobutamine administration results in similar hemodynamic improvements but with no change in left ventricular mechanical efficiency and with opposite effects on lactate metabolism. The opposing metabolic actions, yet similar hemodynamic responses, of dichloroacetate and dobutamine suggest that these agents may be complementary in the treatment of congestive heart failure.

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Congestive heart failure is associated with impaired mechanical performance of the left ventricle. Whether the cause of heart failure is ischemic heart disease or previous myocardial infarction, congenital or valvular heart disease or a primary disorder of cardiac muscle, interstitial fibrosis is generally present, which decreases the number of contractile proteins available for myocardial contraction (1). Two compensatory mechanisms for interstitial fibrosis and impaired contractility are volume retention and myocyte hypertrophy (1,2). Volume retention improves the loading conditions of the left ventricle by means of the Frank-Starling mechanism (2). Myocyte hypertrophy improves contractility by increasing the total mass of myocardial tissue available for contraction (3). It also reduces wall stress by increasing the wall thickness of an otherwise dilated chamber (4).

Unfortunately, cavitary enlargement, myocyte hypertrophy and increased wall thickness combine to more than double left ventricular mass in chronic heart failure (4,5). Myocardial oxygen requirements increase commensurately even though developed pressure and stroke and minute work

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are generally subnormal (4–9). Left ventricular mechanical efficiency thus declines and is typically 15% in chronic heart failure, whereas it is as high as 40% in normal subjects or patients with coronary artery disease without heart failure (10).

Sodium dicholoroacetate is an investigational agent that stimulates pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase (11). Stimulation of pyruvate dehydrogenase with dichloroacetate occurs in most tissues, particularly the myocardium (11,12). Stimulation of pyruvate dehydrogenase activity with dichloroacetate leads to enhanced glycolysis of glucose and utilization of lactate by the myocardium for aerobic respiration (11,12). Myocardial consumption of free fatty acids is simultaneously inhibited, with the overall effect of a change of substrate utilization from predominantly nonesterified free fatty acids to glucose and lactate (11–16). The mechanical efficiency of the left ventricle should thus improve with dichloroacetate to the extent that high respiratory quotient glucose and lactate are consumed preferentially over low respiratory quotient nonesterified free fatty acids (17–22). In preliminary studies in patients with coronary artery disease and normal left ventricular function, improvements in left ventricular mechanical efficiency were achieved with dichloroacetate administration (23). Forward stroke volume and cardiac output increased at the same time that myocardial oxygen consumption decreased. Myocardial mechanical efficiency improved as a result (23).

The present study was thus undertaken to assess whether dichloroacetate improves left ventricular mechanical efficiency and hemodynamic performance of the failing left ventricle in patients with congestive heart failure.

Methods

Patients. Ten patients with New York Heart Association functional class III to IV congestive heart failure were studied. The underlying cause of congestive heart failure was coronary artery disease in seven patients and idiopathic dilated cardiomyopathy in three. All patients were studied while in hospital for the management of congestive heart failure at the University of California, Moffitt Hospital, San Francisco, California. This study was approved by the Institutional Review Board of the University of California, San Francisco, and informed consent was obtained for each patient.

Study protocol. Pulmonary artery and coronary sinus catheters were placed using standard percutaneous techniques, and proper positioning was confirmed by fluoroscopy. Cardiac indexes (liters/min per m^2 body surface area) were determined by the thermodilution technique (24) with the patient supine in the fasting state. A minimum of three determinations were made for each patient, and these were averaged to obtain a single value. Coronary blood flow (ml/min) was estimated by continuous thermodilution (25) using Wilton-Webster coronary sinus catheters and infusion of room temperature 5% dextrose in water at a rate of 46 ml/min. Oxygen saturation of arterial, pulmonary arterial and coronary sinus blood were measured directly with a hemoximeter (Radiometer, model OSM-2). Blood gases were measured for arterial, mixed-venous and coronary sinus blood using automated blood gas analyzers (Corning Medical, models 168 and 178). Hemoglobin content was measured by the cyanmethemoglobin method. Blood lactate concentration was measured using the NAD/NADH assay method for samples deproteinized in perchloric acid. Glucose concentration was measured using a glucose analyzer.

Analysis of dichloroacetate in plasma. Gas chromatography was used to analyze dichloroacetate. Briefly, plasma (100 μl) is transferred to a 16- × 100-mm screw-cap culture tube (Kimax). To this, 50 μl of a 50-μg/ml solution of trichloroacetic acid (internal standard) is added, followed by 1 ml of 14% of boron trifluoride in methanol. The culture tube is vortexed briefly and then heated to 100°C for 15 min. Cyclohexane (1 ml) and water (1 ml) are added to the mixture and agitated for 10 min (Lab-Line shaker), followed by centrifugation for 10 min (~2,500 × g). The organic layer (top 1 μl) is injected into a Varian 3600 gas chromatograph equipped with a 6-ft (1.8 m) × 2-mm inner diameter Chromosorb 101 column, a nitrogen-63 electron capture detector and a Nelson Analytical 2600 chromatographic integrator. The column temperature is 160°C. The peak areas obtained from the integrator are used in the determination of the ratio of dichloroacetate to trichloroacetate. Every batch of dichloroacetate analysis involved calibration with known mixtures of dichloroacetate in plasma (2.5 to 200 μg/ml) and trichloroacetate. The calibration graph was linear.

Calculations. Measured oxygen content was obtained from the directly measured data using the formula: Oxygen content (vol %) = Oxygen saturation/100 × Hemoglobin content (g/dl) × 1.34 (ml/g) + 0.0031 Partial pressure of oxygen (Po_2) (mm Hg). Systemic oxygen transport (ml oxygen/min per m^2 body surface area) was defined as Arterial oxygen content × Cardiac index × 10. Myocardial oxygen transport (ml oxygen/min) was established similarly as (Arterial oxygen content × Coronary blood flow)/100. Systemic oxygen consumption (Vo_2) (ml oxygen/min per m^2 body surface area) was determined with the formula $Vo_2 = AVDo_2 \times$ Cardiac index × 10, where $AVDo_2$ = arterial-venous oxygen difference. Myocardial oxygen consumption (ml oxygen/min) was estimated similarly, where Myocardial oxygen consumption = Coronary blood flow/100 × (Arterial oxygen content − Coronary sinus oxygen content).

Left ventricular stroke work index (g-m/m^2) was estimated as Stroke work index = (Mean systolic pressure − Pulmonary capillary wedge pressure) × Stroke volume index × 0.0136, where mean systolic and pulmonary capillary wedge pressures and stroke volume index were measured, and 0.0136 is a conversion factor from ml × mm Hg/m^2 to g-m/m^2. Left ventricular minute work was determined by factoring stroke work by heart rate. Left ventric-

ular mechanical efficiency was estimated by the ratio of left ventricular minute work to myocardial oxygen consumption.

Drug infusions. Sodium dichloroacetate, 50 mg/kg, was administered intravenously for 30 min with hemodynamic measurements made every 15 min and blood measurements every 30 min for 2 h. After dichloroacetate infusions on the first day, the patient was allowed to recover overnight to allow metabolism of dichloroacetate before being given intravenous dobutamine infusions on day 2. Dobutamine was then titrated to clinically optimal doses (5.0 to 12.5 μg/kg per min) on the basis of the patient's clinical and hemodynamic response. Measurements of hemodynamic variables, coronary blood flow, blood lactate levels and oxygen consumption were then performed both before and after clinically optimal dosing of dobutamine. The 60-min peak effects of dichloroacetate were compared with the effects of dobutamine once the patient had achieved a steady state during a dobutamine infusion for at least 30 min. Blood sampling and hemodynamic measurements were performed at baseline just before dobutamine infusion and after 30 min of continuous infusion at steady state. The steady-state hemodynamic and blood measurements obtained with dobutamine were then compared with the peak actions of dichloroacetate in the same patients.

Statistical analyses. Statistical analyses were performed using a repeated-measures analysis of variance. Comparisons between the peak effects of sodium dichloroacetate and of intravenous dobutamine were performed using a single paired two-tailed *t* test. Differences between dichloroacetate and dobutamine infusions were considered statistically significant when $p < 0.05$. Power calculations were performed as follows: with an alpha level of 0.05, a power of 80%, a sample size of 10, and a standard deviation of 0.26, one would be able to detect a clinically important difference of 0.23 between baseline and dichloroacetate for cardiac index. Similarly, for left ventricular mechanical efficiency, with a standard deviation of 5.8, a clinical difference of 5.2 could be detected. All statistical analyses were performed using a Macintosh computer and a Statview Statistical Software package (Brain Power, Inc.). The data are presented as mean values ± SE unless otherwise indicated.

Results

Pharmacodynamic variables. Plasma dichloroacetate levels peaked at the end of the 30-min infusion and decreased to plateau levels within 60 min. Plateau levels achieved at 60 min were maintained at 120 min, consistent with a two-compartment distribution with slow elimination kinetics after an early rapid distribution phase (Fig. 1). There was no preferential extraction of dichloroacetate by the myocardium, as arterial, mixed-venous and coronary sinus concentrations of dichloroacetate were the same and showed the same time kinetics (Fig. 1).

Hemodynamic variables. Baseline hemodynamic variables of the patients studied showed the usual hemodynamic

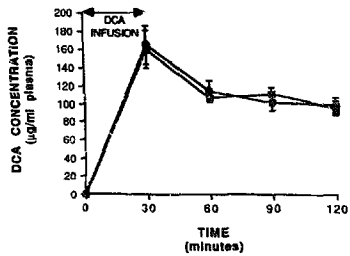


Figure 1. Plasma concentrations of dichloroacetate (DCA) after a 30-min infusion of 50 mg/kg of dichloroacetate. Squares = arterial plasma samples; circles = coronary sinus plasma samples.

profile observed in dilated cardiomyopathy, with a decreased rest cardiac index and stroke volume and elevation of the central venous and left atrial pressures (Table 1). With dichloroacetate, the heart rate, mean arterial, right atrial, pulmonary artery, pulmonary capillary wedge pressures and pulmonary and systemic vascular resistances did not change appreciably. However, cardiac index increased by an average of 15% (from 1.85 to 2.05 liters/min per m^2, $p < 0.02$) (Fig. 2). Stroke volume increased and showed a peak effect at 60 min (net change +5.3 ml/beat, $p < 0.02$) (Fig. 3). Left ventricular stroke work also increased and showed a similar time course, with a peak effect at 60 min (from 14.7 to 16.5 g-m/m^2 per beat, $p < 0.02$). Estimated left ventricular minute work increased from a baseline of 1.38 to 1.55 kg-m/m^2 per min, $p < 0.01$, with a similar peak at 60 min. The peak hemodynamic actions of dichloroacetate thus occurred at 60 min, coincident with the rapid distribution phase of the drug and establishment of plateau drug levels.

Coronary blood flow decreased with administration of dichloroacetate and showed its nadir at 60 min, when forward stroke volume and left ventricular stroke work were at their peak. The trend in coronary blood flow over time

Table 1. Baseline Hemodynamic Variables

Variable	Mean ± SD
Heart rate (beats/min)	95 ± 3
Mean arterial pressure (mm Hg)	83 ± 5
Cardiac index (liters/min per m^2)	1.8 ± 0.2
Stroke volume index (ml/beat per m^2)	19.4 ± 2.0
Pulmonary capillary wedge pressure (mm Hg)	29 ± 1
Central venous pressure (mm Hg)	19 ± 1
Systemic vascular resistance (dynes·s·cm^{-5})	1,631 ± 235
Pulmonary vascular resistance (dynes·s·cm^{-5})	420 ± 82
Coronary blood flow (ml/min)	163 ± 29
Myocardial oxygen consumption (ml oxygen/min)	19.3 ± 2.8

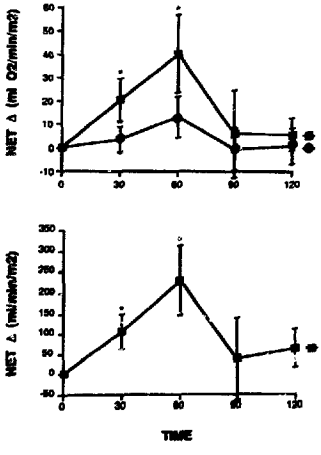


Figure 2. Net changes (Δ) in (top) systemic oxygen transport (squares) and consumption (circles) and (bottom) cardiac index (squares) after dichloroacetate infusion. Net changes from baseline are shown to correct for individual variations in baseline measurements between patients. *p < 0.05.

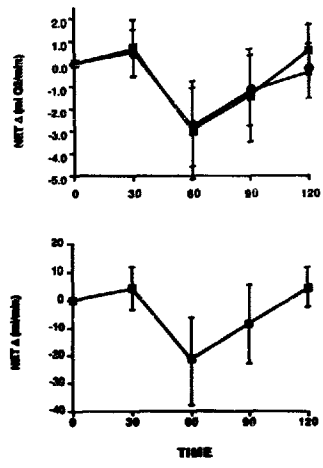


Figure 4. Net changes (Δ) in (top) myocardial oxygen transport (squares) and consumption (circles) and (bottom) coronary blood flow (squares) after dichloroacetate infusion. Note that oxygen transport and consumption are closely correlated to blood flow and that dichloroacetate does not appear to alter oxygen extraction.

mirrored that of forward stroke volume and cardiac output and showed opposite trends (Fig. 4).

Substrate utilization. Blood lactate concentrations were normal at baseline. Myocardial lactate extraction averaged 29%, which is comparable to the percent of lactate extraction seen in normal, nonfailing hearts (8,22,24). With dichloroacetate administration, myocardial lactate extraction increased 8.8% overall to 37.4%, at the same time that arterial lactate levels decreased >50% (Fig. 5). Myocardial lactate extraction ratios were thus maintained as blood lactate

Figure 3. Net changes (Δ) in stroke volume (squares) and pulmonary capillary wedge pressure (circles) after dichloroacetate (DCA) infusion. The simultaneous increase in stroke volume and decrease in pulmonary capillary wedge pressure suggest positive inotropism. *p < 0.05.

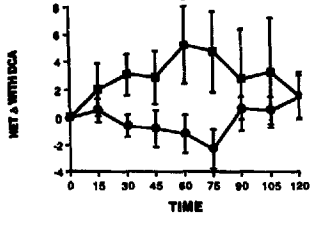
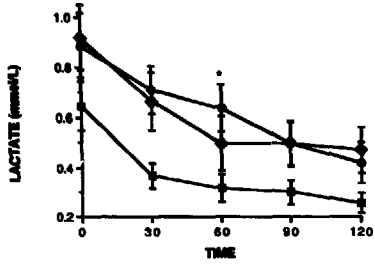


Figure 5. Plasma lactate concentrations after dichloroacetate infusion. Note the continuous decrease in blood lactate concentrations over time. Diamonds = arterial plasma samples; circles = pulmonary artery mixed venous samples; squares = coronary sinus samples.



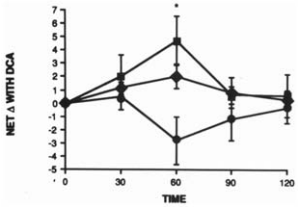


Figure 6. Relation between myocardial work and oxygen consumption (**circles**) after dichloroacetate (DCA) infusion. Note that left ventricular mechanical efficiency improves after dichloroacetate infusion at 60 min. **Squares** = left ventricular mechanical efficiency; **diamonds** = left ventricular stroke work index; Δ = change. *$p < 0.05$.

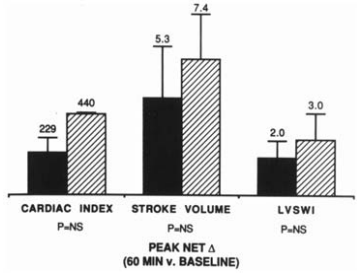


Figure 7. Peak hemodynamic action of dichloroacetate (solid bars) at 60 min versus optimal effects of dobutamine (hatched bars). LVSWI = left ventricular stroke work index; Δ = change.

concentrations decreased, consistent with stimulation of myocardial lactate consumption. Coronary sinus lactate levels reached exceeding low levels, typically in the 0.2 to 0.3-mmol/liter range, consistent with maximal stimulation of lactate consumption by the myocardium. Lactate levels reached their nadir at 60 min of therapy and remained at extremely low levels for the remainder of the 2-h observation period. Conversely, blood glucose concentrations did not change (172 mg/dl at baseline vs. 158 mg/dl at 60 min, p = NS). Coronary sinus glucose concentrations also did not change, such that net myocardial extraction ratios for glucose were unaltered by dichloroacetate.

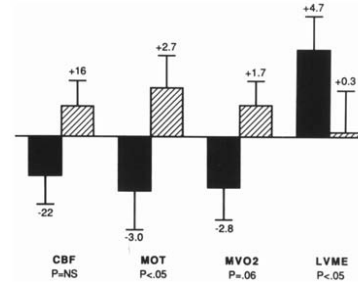
Myocardial oxygen consumption and mechanical efficiency. Baseline myocardial energetics were characterized by high myocardial oxygen consumption, normal left ventricular minute work and low left ventricular mechanical efficiency (15.2%). With dichloroacetate, left ventricular minute work increased as myocardial oxygen consumption decreased. Left ventricular mechanical efficiency increased to 20.6% ($p = 0.03$) (Fig. 6). Approximately half of the improvement in myocardial mechanical efficiency was related to the decrease in myocardial oxygen consumption (maximal change of −18% at 60 min), with the balance of the improvement related to an increase in left ventricular stroke work of similar magnitude (maximal change of +15% at 60 min).

Comparison of dichloroacetate with dobutamine. Cardiac output and forward stroke volume increased similarly with dichloroacetate and dobutamine administration (Fig. 7), but the patterns of substrate utilization were markedly different. Whereas dichloroacetate increased myocardial lactate consumption significantly, dobutamine decreased myocardial lactate extraction and consumption (from 34% to 15.3%, $p < 0.02$). Net positive lactate production was seen in 3 of the 10 patients who received dobutamine, consistent with the development of myocardial ischemia. Myocardial oxygen consumption decreased with dichloroacetate and increased with dobutamine (from 18.6 to 21.0 ml/min, $p = 0.06$). Left ventricular stroke work increased proportionately to the increase in myocardial oxygen consumption with dobutamine such that left ventricular mechanical efficiency did not change (from 16.4% to 15.8%, p = NS) (Fig. 8). In contrast, left ventricular mechanical efficiency improved significantly with dichloroacetate, as noted earlier.

Discussion

Myocardial oxygen requirements with dichloroacetate. Congestive heart failure is associated with impaired mechanical performance of the left ventricle. Impairment of left ventricular systolic function leads to reduction in forward

Figure 8. Peak metabolic actions of dichloroacetate (**solid bars**) versus dobutamine (**hatched bars**). Note the opposite trends in myocardial oxygen consumption (MVO2) and coronary blood flow (CBF) and the significant difference in left ventricular mechanical efficiency (LVME) with the two drugs. MOT = myocardial oxygen transport.



stroke volume. Compensatory changes for reduced forward stroke volume include an increase in left ventricular diastolic volume and mass. Mechanical efficiency declines as a result of the increased oxygen demands imposed by increased wall stress, cavitary enlargement and increased left ventricular mass (4–10,26), not because of fundamental changes in the contractile economy of the left ventricle because the contractile economy of failing myocardium remains essentially normal (Ishihara H, personal communication, January 1993). Oxygen requirements are greater than normal to perform an equivalent amount of cardiac work as a result of this inefficiency (4–10). In the present study, the infusion of 50 mg/kg of dichloroacetate for 30 min was associated with an improvement in stroke volume and mechanical efficiency of the failing left ventricle in patients with congestive heart failure. To our knowledge, this is the first report of a pharmacologic agent that is capable of improving mechanical efficiency in heart failure.

Although vasodilators reduce myocardial oxygen requirements and the improved forward stroke volume, this is largely a result of reduced afterload, lower peak systolic pressure and commensurate reduction in cardiac work, with no overall change in left ventricular mechanical efficiency (27–30). Left ventricular volume also tends to decrease as a result of reduced afterload, which further reduces oxygen requirements (30). Inotropes, on the other hand, increase forward stroke volume and left ventricular work by stimulation of myocardial contractility. Oxygen requirements generally increase linearly with contractility, with no overall change in left ventricular mechanical efficiency (31). In the present study, dobutamine increased forward stroke volume, left ventricular work and myocardial oxygen requirements commensurately such that left ventricular mechanical efficiency did not change.

Mechanisms of action. The manner in which dichloroacetate augments myocardial mechanical performance is speculative. Administration of 50 mg/kg of dichloroacetate for 30 min achieved therapeutic levels of ≥150 μg/liter of dichloroacetate in most patients. Plasma levels of 100 to 200 μg/liter of dichloroacetate are probably sufficient to stimulate pyruvate dehydrogenase activity in most tissues (11,12). Stimulation of the pyruvate dehydrogenase enzyme complex by dichloroacetate has been shown to increase glucose oxidation in cardiac muscle (12,13). Pyruvate dehydrogenase is the principal regulatory enzyme in the pathway controlling entry of glycolytic intermediates (glucose and lactate) into the trichloroacetate cycle for aerobic respiration (11–14). Stimulation of pyruvate dehydrogenase thus accelerates formation of acetyl coenzyme A from pyruvate. Conversion of lactate to pyruvate for aerobic respiration is also facilitated by dichloroacetate in cardiac muscle (12,16,17,23). Lactate consumption is increased generally, and marked reductions in blood lactate concentrations are seen with dichloroacetate administration (32,33). At the same time, oxidation of short- and medium-chain nonesterified fatty acids is inhibited, particularly in the myocardium. A shift from consumption of predominantly nonesterified fatty acids to glucose and lactate results (12–16).

The fact that myocardial lactate extraction was maintained at extremely low blood lactate concentrations is consistent with stimulation of myocardial lactate consumption by dichloroacetate. Although arterial and coronary sinus blood glucose concentrations did not change overall, the normal myocardium is known to extract only a small fraction (18%) of delivered blood glucose under basal conditions (22). Increases in myocardial glucose consumption would not be expected to alter coronary sinus glucose concentrations appreciably because baseline extraction ratios are so low. Radiolabeled glucose uptake measurements would be required to determine whether or not myocardial glucose uptake and metabolism were increased with dichloroacetate (16), which was beyond the scope of this study.

Enhancement of glucose and lactate oxidation by the myocardium could explain the increase in left ventricular mechanical efficiency seen with dichloroacetate administration. Cardiac muscle, both normal and failing, preferentially consumes nonesterified fatty acids over glucose and lactate. Nonesterified fatty acids, although a rich fuel source for aerobic respiration, are a relatively inefficient fuel source, yielding only 2.8 mol of adenosine triphosphate per mole of nonesterified fatty acids consumed (low respiratory quotient of 0.7) (22). Glucose and lactate, on the other hand, are more efficient fuels for aerobic respiration, yielding 3.0 to 3.2 mol of adenosine triphosphate per mole of glucose or lactate consumed (high respiratory quotient of 1.0) (22). Switching myocardial substrate utilization from low to high respiratory quotient fuels could theoretically yield a 16% to 26% improvement in the oxygen consumption efficiency of the myocardium (12,32). This is strikingly similar to the actual measured improvement of mechanical efficiency observed with dichloroacetate, which occurred at 60 min (from 16.1% at baseline to a peak of 20.6% at 60 min, a 28% increase compared with baseline values). Although not rigorously proved, it is suggested that the improvement seen in left ventricular mechanical efficiency in this study is related to the metabolic effects of dichloroacetate, switching cardiac muscle from primary nonesterified fatty acid consumption to glucose and lactate consumption.

Time kinetics. Why left ventricular mechanical efficiency declined after 60 min is not known. Although plasma levels of dichloroacetate peaked at 30 min at the end of the infusion, they remained relatively constant in the 100- to 120-mmol/liter range during the 2-h observation period (Fig. 1). Despite therapeutic plasma levels of dichloroacetate for the entire 2 h, left ventricular mechanical efficiency peaked at 1 h and declined toward baseline levels thereafter. One possible explanation may be that lactate levels were driven to such low levels by dichloroacetate that little remained for consumption in the second hour, leading to "substrate burnout." Against this possibility is the fact that blood glucose concentrations did not change. Whether the hemodynamic and metabolic benefits of dichloroacetate could be

extended beyond 60 min by fueling the myocardium with more substrate (i.e., with supplemental glucose, lactate or pyruvate infusions) is not known. Also, this small pilot study may not be sufficiently powerful to detect small improvements in hemodynamic and metabolic function beyond 60 min. The precise reason for the increase and decrease in left ventricular mechanical efficiency during 2 h after dichloroacetate administration remains unexplained.

The hemodynamic actions of dichloroacetate demonstrated a similar increase and decrease during the 2-h observation period and also peaked at 60 min. The increase in forward cardiac index observed appears to result from a primary increase in forward stroke volume because stroke volume increased progressively at the same time that pulmonary capillary wedge pressure fell, with a peak at 60–75 min (Fig. 3). The increase in cardiac output appears to be unrelated to volume loading because the volume administered was small (~50 ml), and pulmonary capillary wedge pressure actually declined during the dichloroacetate infusions.

Whether the increase in stroke volume was caused by a direct inotropic action, a primary reduction in afterload or a combination of these actions cannot be determined from the data obtained in this study. Studies in patients with coronary artery disease and in isolated perfused rat hearts with endotoxic stress or coronary occlusion have shown evidence for primary stimulation of myocardial contractility with dichloroacetate (16,18,19,23,34,35). Although a primary vasodilating action of dichloroacetate has also been described, this appears to be due to the ganglionic blocking properties of the diisopropyl ammonium salt of dichloroacetate, not to dichloroacetate itself (11). The sodium salt of dichloroacetate has not been associated with hypotension when used clinically (11,32,33), but the direct effects of dichloroacetate on vascular smooth muscle have not been characterized.

Conclusions. Whether dichloroacetate exhibits inotropism or vasodilation or both, the magnitude of the effect of dichloroacetate on forward stroke volume and stroke work is similar to that of clinically optimal doses of intravenous dobutamine. The striking aspect of dichloroacetate's actions is that such hemodynamic improvements in the failing myocardium can be achieved with a net reduction in myocardial oxygen consumption, with a resultant improvement in left ventricular mechanical efficiency. In contrast, myocardial oxygen consumption increases commensurately with any increase seen in left ventricular work stimulated by dobutamine, and there is no change in overall mechanical efficiency. Because beta-adrenergic stimulation is associated with increased myocardial extraction of nonesterified fatty acids and reduced consumption of glucose and lactate (the opposite of what occurs with dichloroacetate), a metabolic basis for opposing effects of dobutamine and dichloroacetate on left ventricular mechanical efficiency is suggested. One would predict that inotropes and dichloroacetate might well be complementary and have additive effects on hemodynamic performance (36). Further studies thus appear warranted to assess whether dichloroacetate is useful as an adjunct to beta-adrenergic stimulation in the treatment of congestive heart failure.

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