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Clinical Investigations

Effects of Dichloroacetate in Patients with Congestive Heart Failure

JANNET F. LEWIS, M.D., MICHELLE DACOSTA, B.S., THOMAS WARGOWICH, M.D., PETER STACPOOLE, PH.D., M.D.

Divisions of Cardiovascular Medicine and Endocrinology and Metabolism, Department of Medicine and the Department of Biochemistry and Molecular Biology, University of Florida College of Medicine, Gainesville, Florida, USA

Summary

Background: Conventional approaches to management of congestive heart failure (CHF) rely on drugs that increase myocardial contractility or reduce ventricular afterload. These approaches often improve cardiac symptoms and survival, but may be associated with significant deleterious effects. An alternative approach is to enhance myocardial energy production. Dichloroacetate (DCA) stimulates pyruvate dehydrogenase activity and accelerates aerobic glucose, pyruvate, and lactate metabolism in myocardial cells. These alterations would be expected to improve myocardial function.

Hypothesis: The purpose of the investigation was to assess the efficacy of DCA in patients with left ventricular systolic dysfunction and to examine the mechanism by which improvement occurs.

Methods: A total of 25 patients (16 men, 9 women; age range 31–72 years, mean 59) with CHF and ejection fraction ≤40% received an intravenous infusion of 50 mg/kg DCA over 15 min. Indices of systolic and diastolic function were obtained by two-dimensional and Doppler echocardiography performed at baseline, 30 min, and 60 min following completion of DCA infusion.

Results: Baseline ventricular ejection fraction was 27.3 ± 9.1%; 17 patients (68%) had nonischemic cardiomyopathy. Heart rate increased after DCA infusion from 73.9 ± 14.5 to 79.2 ± 14.9 beats/min at 60 min; p = 0.02. Left ventricular diastolic and systolic volumes increased at 30 min compared with baseline (248.7 ± 98.1 vs. 259.6 ± 99.6; p = 0.04, and 180.1 ± 80.4 vs. 192.2 ± 84.9; p = 0.002, respectively), but stroke volume (49.2 ± 19.1 vs. 48.9 ± 18.1; p = 0.9) and ejection fraction (27.3 ± 9.1 vs. 25.7 ± 9.8; p = 0.2) were unchanged. Indices of diastolic function were also unchanged.

Conclusion: Dichloroacetate infusion in patients with CHF is not associated with improvement in noninvasively assessed left ventricular function.

Key words: heart failure, dichloroacetate, echocardiography

Introduction

Congestive heart failure (CHF) is associated with impaired mechanical performance of the left ventricle. Conventional pharmacologic management of CHF has generally focused on agents that increase myocardial contractility by direct stimulation[1–4] or by vasodilators that cause afterload reduction.[5–7] These approaches, while substantially improving symptoms and survival, are not applicable to many patients because of deleterious side effects or contraindication in those with coexistent disease. In addition, positive inotropic agents, while improving contractility, also increase myocardial oxygen consumption.[8–10] An alternative approach involves the use of agents that alter myocardial metabolism.

Dichloroacetate (DCA) is an investigational drug that rapidly stimulates the activity of the pyruvate dehydrogenase multienzyme complex,[11] thereby accelerating aerobic glucose, pyruvate, and lactate metabolism in myocardial and other cells. In cardiac tissue, DCA also inhibits long chain fatty acid oxidation, thus increasing the proportion of carbohydrate utilized for energy production.[12] This alteration in myocardial metabolism would be expected to improve myocardial function without increasing oxygen consumption, since approximately 14% more adenosine triphosphate (ATP) is generated per mole of oxygen consumed when cells oxidize glucose in preference to fatty acids. Preliminary studies in patients with coronary artery disease[13] and CHF[14] demonstrated that intravenous DCA increased stroke volume and cardiac index. The purpose of the present investigation was to assess the efficacy of DCA further in patients with left ventricular systolic dysfunction and to examine the mechanism by which improvement occurs.

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Address for reprints:

Jannet F. Lewis, M.D.
1600 Archer Road
P.O. Box 100277
Gainesville, FL 32610-0277, USA

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Methods

Patients with left ventricular ejection fraction ≤40% and technically adequate echocardiograms were recruited for study if they met the following criteria: (1) age > 21 years, (2) stable heart failure symptoms, (3) no change in medications for at least 2 weeks, and (4) absence of unstable angina or myocardial infarction within 2 months of study. Patients who were clinically unstable, had atrial fibrillation, congenital heart disease, or primary valvular heart disease were excluded. The protocol was approved by the University of Florida Institutional Review Board, and each patient gave verbal and written informed consent. The initial protocol submitted to the Institutional Review Board requested inclusion of 30 patients. However, recruitment was terminated after Patient No. 25 following preliminary data analysis in the first 20 patients.

Patients were admitted to the General Clinical Research Center the evening prior to study to monitor blood pressure and assure clinical and hemodynamic stability. All medications were held after 12:00 A.M. Each subject underwent baseline two-dimensional (2-D) and Doppler echocardiography using commercially available equipment [HDI 3000, Advanced Technology Labs (ATL), Bothell, Wash., USA]. The patient then received an intravenous infusion of 50 mg/kg DCA in saline over 15 min. Blood pressure and heart rate were monitored and recorded every 15 min. Complete 2-D and Doppler echocardiography studies were repeated 30 min, and 60 min following completion of drug infusion. Baseline, 30 min, and 60 min studies were recorded on three separate ½" videotapes for subsequent review and analysis. Analysis of studies was performed by an experienced echocardiographer (JFL) blinded to the timing and sequence of the echocardiography study.

Measurements were made off-line on a computer workstation (Datavue, NovaMicrosonics, Indianapolis, Ind., USA). These included left ventricular diastolic and systolic volumes (using biplane method of discs algorithm from the apical 4- and 2-chamber views),[15] ejection fraction (from calculated 2-D volumes), indices of diastolic filling from Doppler-derived mitral inflow velocity,[16, 17] including peak E and peak A velocities, integrals of early and late velocities, E deceleration time, and indices from pulmonary vein flow velocity[18, 19] including peak systolic and peak diastolic forward flow, peak velocity, and duration of reversal of flow in late diastole. Stroke volume and cardiac output were calculated from the left ventricular outflow diameter and pulsed Doppler using previously described methods.[20]

Statistical Analysis

Continuous variables are expressed as mean ± 1 standard deviation. Blood pressure, heart rate, left ventricular volumes, and indices of systolic and diastolic function were compared at baseline, 30 min, and 60 min after drug infusion using analysis of variance (ANOVA). Intraobserver reproducibilty for left ventricular diastolic and systolic volumes have previously been reported as 11 and 15%, respectively.[21] Pulmonary vein flow and tricuspid regurgitant jet velocities were reliably obtained at baseline and after infusion in only four patients (because of the absence of significant tricuspid regurgitation or difficulty in obtaining high quality waveforms in subjects with left ventricular dilation) and are not included in the analysis. Differences from baseline to postinfusion were considered significant when $p < 0.05$. Statistical analyses were performed using a commercially available statistical package (SAS Institute, Inc., Cary, N.C., USA).

Results

In all, 25 patients were recruited for study. Patients ranged in age from 31 to 72 years (mean 59); 16 (64%) were men and 9 (36%) were women. Most patients (17, 68%) had nonischemic cardiomyopathy, documented by cardiac catheterization and coronary arteriography, and the remaining 8 had severe coronary artery disease involving ≥ one major vessel. All patients were on intensive medical treatment that included a combination of digoxin, diuretics, and angiotensin-converting enzyme inhibitors or angiotensin II blockers; five patients were also taking beta-adrenergic blocking agents. No major complications occurred during DCA infusion. Brief somnolence, previously reported during DCA administration,[11] was observed in five subjects, but could not clearly be attributable to the infusion since the study was performed in the early morning under quiet conditions.

Baseline left ventricular systolic function was severely impaired in all patients; mean ejection fraction was 27.3 ± 9.1%. Table I summarizes the hemodynamic findings at baseline, and at 30 min and 60 min following DCA infusion. Heart rate increased slightly from 74.0 ± 14.5 beats/min at baseline to 77.2 ± 16.1 at 30 min following DCA infusion ($p = 0.1$), and to 79.2 ± 14.9 at 60 min ($p = 0.02$) (Fig. 1). Left ventricular diastolic and systolic volumes also increased at 30 min after infusion, but were not different at 60 min (Fig. 2). Measures of systolic function (ejection fraction, stroke volume, and cardiac output) (Fig. 3) and indices of left ventricular diastolic function were unchanged from baseline to 30 min and 60 min after infusion.

Discussion

Congestive heart failure due to left ventricular systolic dysfunction is associated with compensatory left ventricular dilation, increased wall stress, and hypertrophy.[9] These compensatory responses result in increased myocardial oxygen consumption and reduced myocardial efficiency.[22, 23] Inotropic agents used in the management of patients with CHF improve myocardial contractility, but are also associated with increased myocardial oxygen consumption.[24] Shifting myocardial metabolism from predominantly long chain fatty acids to glucose utilization might be expected to improve cardiac function in patients with CHF due to a theoretical increase in ATP production for the same rate of myocardial

TABLE I Noninvasive hemodynamic findings in patients with severe left ventricular systolic dysfunction receiving dichloroacetate infusion

	Baseline	30 min	60 min	p Value[a]
SBP (mmHg)	115.6 ± 19.0	116.8 ± 17.2	114.4 ± 17.1	0.42
DBP(mmHg)	70.3 ± 12.8	69.6 ± 10.8	67.1 ± 10.3	0.77
Heart rate (beats/min)	73.9 ± 14.5	77.2 ± 16.1	79.2 ± 14.9[b]	0.14
LVDV (ml)	248.7 ± 98.1	259.6 ± 99.6	243.7 ± 103.2	0.04
LVSV (ml)	180.1 ± 80.4	192.2 ± 84.9	177.1 ± 82.2	0.002
Stroke volume (ml)	49.2 ± 19.1	49.0 ± 18.1	45.8 ± 21.1	0.9
Cardiac output (l/m)	3.54 ± 1.43	3.86 ± 1.66	3.24 ± 1.44	0.18
Ejection fraction (%)	27.3 ± 9.1	25.7 ± 9.7	26.5 ± 8.7	0.27
Mitral E/A ratio	1.5 ± 1.1	1.4 ± 0.93	1.5 ± 1.1	0.65
DCT (ms)	157.8 ± 47.1	155.7 ± 47.0	149.6 ± 37.8	0.89

[a] Values for 30 min post infusion versus baseline; values at 60 min not statistically different from baseline with exception of heart rate.
[b] p = 0.02.
Abbreviations: DCT = mitral E deceleration time, DBP = diastolic blood pressure, LVDV = left ventricular end-diastolic volume, LVSV = left ventricular end-systolic volume, SBP = systolic blood pressure, mitral E/A ratio = ratio of peak E and peak A velocities.

oxygen consumption.[25-27] Our findings do not support previous observations[13, 14] that DCA is efficacious in this regard.

Dichloroacetate is a potent activator of pyruvate dehydrogenase, the mitochondrial enzyme that oxidizes pyruvate to acetyl CoA and catalyzes the rate-determining step in aerobic metabolism of glucose, pyruvate, and lactate.[11] As recently reviewed,[12] DCA stimulates aerobic glucose oxidation and inhibits fatty acid oxidation in isolated, perfused animal heart preparations following induction of fasting,[28] diabetes mellitus,[29] endotoxemia,[30] and in the canine heart in situ following coronary artery occlusion.[31] In hearts from animals with endotoxemia, DCA stimulated pyruvate dehydrogenase activity and glucose and lactate oxidation restored ATP concentrations and increased stroke work, cardiac output, and peak systolic pressure development over a range of filling pressures.[32] Dichloroacetate has also been shown to enhance the inotropic effects of ouabain and amrinone in hearts from rats given endotoxin.[33]

Preliminary clinical studies have also suggested a beneficial effect of DCA on myocardial function. In patients with angina and coronary artery disease undergoing cardiac catheterization, DCA infusion was associated with increased stroke volume.[13] Bersin *et al.* also demonstrated increased stroke volume and stroke work in 10 patients with CHF following infusion of DCA.[14] This increased stroke volume and stroke work was accompanied by a decreased myocardial oxygen consumption and therefore improved myocardial efficiency. Our findings differ from those of Bersin *et al.* since we found no appreciable increase in stroke volume or cardiac output in patients with heart failure who received DCA. The discrepancies in these data may in part be due to differences in patient populations. Most patients studied by Bersin *et al.* had CHF due to coronary artery disease, while the majority of our subjects, about 70%, had nonischemic dilated cardiomyopathy. It is also noteworthy that mean cardiac index measured by thermodilution increased by 15%, and net change in stroke volume observed was 5.3 ml/beat, a statistically significant but clinically small change. It is likely that the echocardiographic techniques used in our study would not have detected these small changes.

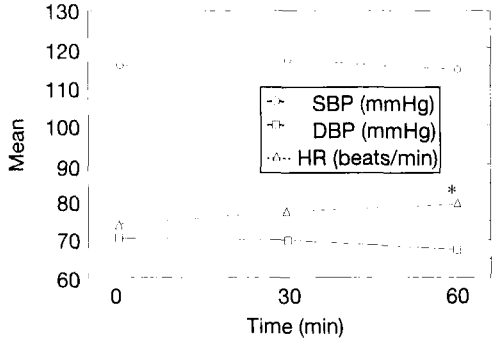

FIG. 1 Hemodynamic changes following dichloroacetate infusion. Time zero marks end of infusion. DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure. *p = 0.02.

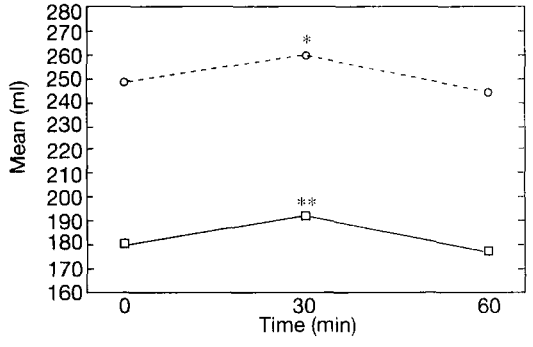

FIG. 2 Effect of dichloroacetate on left ventricular volume. *p = 0.04; **p = 0.002. -o- = left ventricular end-diastolic volume, -□- = left ventricular end-systolic volume.

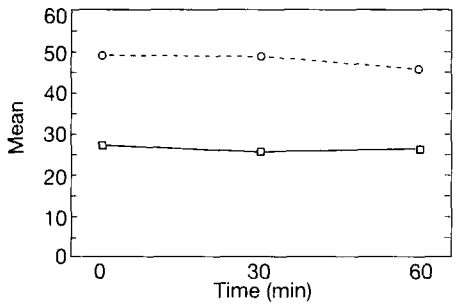

FIG. 3 Effect of dichloroacetate on left ventricular systolic function. -o- = stroke volume (ml), -□- = ejection fraction (%).

There are several potential limitations to the present study that may have influenced our findings. The relatively small number of patients investigated may not be adequate to show small changes in cardiac function following DCA infusion; however, our findings do not suggest any trends that might prove significant in a larger number of patients. Medications were discontinued at least 8 h prior to study, but it is likely that the effects of medications were present at the time of study. In particular, 20% of patients were taking beta-adrenergic blocking agents. The effect of beta blockade could be expected to have persistent cardiovascular hemodynamic effects and hence may have influenced the findings. Finally, measurement of stroke volume and cardiac output by Doppler echocardiography has an observed variability of approximately 16%,[20] and it is possible that small changes may not have been detected with this methodology.

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