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Myocardial Energetics and Clinical Response to the Cardiotonic Agent MDL 17043 in Advanced Heart Failure

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Cardiotonic agents may prove useful in the long-term treatment of chronic heart failure provided myocardial efficiency is enhanced and clinical status is improved. Accordingly, the short-term hemodynamic and clinical response to the phosphodiesterase inhibitor, MDL 17043, was evaluated. Intravenous increments of 0.05 mg/kg (maximal total 3 mg/kg) were given to a peak cardiac output response in 13 patients with New York Heart Association functional class IV heart failure secondary to ischemic or myopathic disease. Significant ($p < 0.05$) responses at peak effect (1.7 mg/kg) included an increase in cardiac output (3.5 to 4.6 liters/min) and heart rate (86 to 90 beats/min) and a decrease in pulmonary capillary wedge (25 to 17 mm Hg), mean arterial (85 to 78 mm Hg) and right atrial (10 to 7 mm Hg) pressures. Coronary sinus flow (measured in nine patients) increased (122 to 144 ml/min, $p < 0.01$) as did myocardial oxygen uptake (14.1 to 15.1 ml/min, $p < 0.01$), whereas myocardial extraction of oxygen (78 to 72%, $p < 0.01$) and lactate (24 to 9%, $p < 0.01$) decreased with three patients producing lactate at the time of their peak cardiac output response. Nine of the 12 patients given long-term oral therapy improved at least one functional class at 2 weeks. This improvement was sustained at 20 weeks in five patients.

Thus, MDL 17043 acutely improves the function of the failing heart. However, the decrease in oxygen extraction occurring with increased myocardial oxygen uptake suggests that intracoronary shunting may occur along with an increase in oxygen demand and contribute to myocardial anaerobiosis in some patients. Hence, to assure an optimal response in myocardial energetics to MDL 17043, individual dose titration and hemodynamic monitoring are recommended.

Despite standard medical therapy with digitalis and various diuretic agents, many patients with chronic heart failure remain symptomatic at rest or with minimal exertion. These patients with advanced heart failure require additional medical therapy to improve ventricular pump function and ameliorate their symptoms. Vasodilator agents, although providing acute salutary hemodynamic benefits, have not proven uniformly effective in the long-term management of these patients. As a result, a variety of cardiotonic agents with positive inotropic and, in some cases, vasodilator properties have been developed in the hope of filling this therapeutic void (1).

MDL 17043, a phosphodiesterase inhibitor with both positive inotropic and vasodilator properties (2–4), is a new agent that improves impaired pump function (2,5); its ability to improve symptomatic status with long-term treatment, however, has not been reported. In addition, a major concern surrounding the use of this and other cardiotonic agents is their potential to increase myocardial oxygen utilization relative to oxygen availability. This would result in myocardial anaerobiosis and adversely affect cardiac performance. Accordingly, our evaluation of MDL 17043 in patients with advanced heart failure was designed to evaluate the following: 1) the hemodynamic response to the intravenous administration of the compound and the corresponding response in myocardial energetics; and 2) the efficacy and safety of oral MDL 17043 in the long-term management of these patients.

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Methods

Study patients. Thirteen patients with congestive heart failure were studied (Table 1). All were in New York Heart Association functional class IV; 10 patients were so debilitated as to be chronically bedridden. All were limited by dyspnea and fatigue; none had angina. The cause of heart

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Table 1. Data on 13 Study Patients

Case	Age (yr) & Sex	Cause of Heart Failure	Cardiac Rhythm	EF (%)	LVID (cm)
1	55 M	VHD	NSR	26	8.1
2	48 M	IHD	NSR	15	7.2
3	63 M	IHD	NSR	8	–
4	60 M	IHD	NSR	21	6.0
5	69 F	IHD	NSR	17	6.8
6	69 M	IHD	NSR	13	–
7	63 M	IHD	NSR	13	–
8	60 M	IHD	AF	12	6.5
9	48 M	IHD	NSR	15	6.8
10	75 M	VHD	AF	10	6.5
11	41 F	ICM	NSR	23	–
12	67 F	ICM	NSR	19	8.2
13	63 M	IHD	NSR	–	5.7
Mean	60			16	6.9
±SD	±10			±5	±0.9

AF = atrial fibrillation; EF = ejection fraction; F = female; ICM = idiopathic congestive cardiomyopathy; IHD = ischemic heart disease; LVID = left ventricular internal dimensions at end-diastole; M = male; NSR = normal sinus rhythm; VHD = valvular heart disease.

failure was ischemic heart disease in nine patients, idiopathic congestive cardiomyopathy in two and severe aortic or mitral valvular incompetence in two. This was confirmed by cardiac catheterization in all but one patient with idiopathic congestive cardiomyopathy. This patient had no history of angina or myocardial infarction. The electrocardiogram showed no evidence of scarring, and there were no regional wall motion abnormalities on noninvasive testing. Ten of the patients were male and three were female; the age range was 41 to 75 years. The mean (±SD) ejection fraction determined by gated blood pool scan was 16 ± 5% and the mean (±SD) echocardiographic left ventricular internal dimension at end-diastole was 6.8 ± 0.8 cm. Ten patients had normal sinus rhythm and three had atrial fibrillation.

All patients were hospitalized a minimum of 3 days before the acute hemodynamic study. During this stabilization phase, adjustments in diuretic and digitalis dosage were carried out to maximize standard therapy, whereas all vasodilating agents other than captopril were discontinued. Captopril was continued in four patients because, despite continued debility, they were thought to have had a beneficial response to this agent. Every attempt was made to achieve a stable medical regimen to compare with the subsequent clinical response to the investigational drug.

Short-term drug study. Written informed consent was obtained from all patients. Patients came to the cardiac catheterization laboratory in the postabsorptive state having received 5 mg of oral diazapam. A triple lumen thermodilution Swan-Ganz catheter was inserted in the right femoral vein and positioned in the pulmonary artery. A thermodilution coronary sinus flow catheter (Wilton-Webster Laboratories) was inserted into the right basilic vein and positioned in the coronary sinus just proximal to the insertion of the most proximal marginal vein. This position was confirmed by contrast injection, and a stable position was assured throughout the study by fluorscopy. In addition, careful attention was directed toward the thermodilution signal to assure that a signal indicative of coronary sinus reflux did not occur. An arterial catheter was inserted percutaneously and positioned in the abdominal aorta.

Baseline arterial, pulmonary artery and coronary sinus samples were obtained for oxygen content. Arterial and coronary sinus samples were also obtained for lactate concentration. Systemic arterial, pulmonary capillary wedge, pulmonary artery and right atrial pressures were recorded in duplicate before the administration of MDL 17043. Thermodilution coronary sinus blood flow was measured by the method of Ganz et al. (6) as previously reported for this laboratory (7). Cardiac output was calculated by thermodilution and by the Fick principle assuming an oxygen consumption of 3.3 cc/min per kg as previously validated in our laboratory (8) in patients with class III and IV congestive heart failure.

MDL 17043 was then administered intravenously in divided doses of 0.5 mg/kg and infused at a rate of 12.5 mg/min every 20 minutes. The blood samples and hemodynamic measurements obtained in the baseline state were repeated immediately and 10 minutes after each dose. Further dosing was discontinued when additional medication failed to increase the cardiac output by 10% or when a maximal dose of 3 mg/kg was achieved.

Calculated values. The following were derived from measured variables:

$$\textit{Coronary vascular resistance (units)} = \frac{\text{Mean arterial pressure}}{\text{Coronary sinus blood flow}}.$$

Rate-pressure product (units) = Systolic arterial pressure × Heart rate.

Myocardial lactate extraction (%)

$$= \frac{(\text{Arterial lactate} - \text{Coronary sinus lactate})}{\text{Arterial lactate}} \times 100\%.$$

Myocardial oxygen extraction (%)

$$= \frac{\begin{pmatrix}\text{Arterial} & \text{Coronary sinus}\\ \text{oxygen content} & - \text{oxygen content}\end{pmatrix}}{\text{Arterial oxygen content}} \times 100\%.$$

Myocardial oxygen consumption (ml/min) = Coronary sinus blood flow × (Myocardial arterial − Coronary sinus oxygen difference).

Assays. Blood for lactate determination was deproteinized in iced 10% prechloric acid and assayed on the same day using a spectrophotometric technique (9). Normal values in our laboratory are 3 to 12 mg/dl. Normal myocardial lactate extraction in our laboratory is 24 ± 5% at rest. Blood oxygen content was measured by co-oximeter (Instrumentation Laboratories) precalibrated with human blood.

Clinical evaluation of long-term therapy. On the hospital day after the demonstration of acute hemodynamic efficacy, patients received an oral dose of MDL 17043 equivalent on an mg/kg basis to the intravenous dose that produced the peak cardiac output response in the catheterization laboratory, provided that myocardial lactate production did not occur. The patients who demonstrated myocardial lactate production at the peak cardiac output response received the next lower dose of MDL 17043 that did not result in myocardial lactate production. This dose was administered as a liquid suspension of 30 mg/ml at a dosing interval of 8 hours. Concomitant medications given before catheterization were reinstituted. The MDL 17043 dose was subsequently increased in three patients at week 8 or 12 when new information about the bioavailability of oral MDL 17043 became available.

Patients were examined daily by the same investigators and the degree of dyspnea, orthopnea, fatigue and edema was assessed. The hospitalization phase of the study continued until the patient's body weight and medical regimen had been stable for a minimum of 2 days and they were walking comfortably in their room. An electrocardiogram and laboratory battery of blood tests were performed on all patients before hospital discharge.

Outpatient visits were weekly for 4 weeks and every 2 to 3 weeks thereafter and were conducted by a single investigator. Clinical evaluation included review of symptoms and a diary of daily weight and physical activity, physical examination, electrocardiogram, laboratory blood tests and urinalysis. Concomitant medications were also recorded.

Statistical analysis. Changes in hemodynamic and metabolic variables were assessed with the *t* test for paired data. A probability of less than 0.05 was considered significant. All values are expressed as mean ± standard deviation.

Results

Systemic hemodynamics. The systemic hemodynamic responses to MDL 17043 at the peak cardiac output response are summarized in Table 2. The peak increase in cardiac index (1.9 ± 0.5 to 2.6 ± 0.6 liters/min by Fick measurement [$p < 0.001$] and 2.1 ± 0.7 to 2.9 ± 0.6 by thermodilution [$p < 0.001$]) occurred at an average dose of 1.7 ± 0.6 mg/kg (range 1.0 to 2.5). This was associated with decreases in pulmonary capillary wedge (25 ± 10 to 17 ± 9 mm Hg, $p < 0.05$), pulmonary artery systolic (49 ± 15 to 41 ± 15 mm Hg, $p < 0.01$) and right atrial (10 ± 5 to 7 ± 4 mm Hg, $p < 0.05$) pressures as well as in arterial mean (85 ± 11 to 78 ± 11 mm Hg, $p < 0.05$), systolic (122 ± 19 to 116 ± 18 mm Hg, $p < 0.01$) and diastolic (70 ± 12 to 61 ± 11 mm Hg, $p < 0.01$) pressures. In addition, a slight but significant ($p < 0.05$) increase occurred in heart rate (86 ± 15 to 90 ± 15 beat/min).

Coronary blood flow and myocardial oxygen consumption. These variables were measured in 9 of the 13 patients. One patient refused these measurements and in another three patients these measurements could not be obtained because of technical considerations. In the nine patients in whom coronary blood flow was measured, MDL 17043 did not alter the rate-pressure product (10,520 ± 1,120 versus 10,500 ± 1,560 mm Hg beats/min^{-1}). Nonetheless, coronary blood flow increased from 122 ± 33 ml/min in the basal state to 144 ± 35 ml/min ($p < 0.01$) at the peak elevation in cardiac output (Fig. 1). Since coronary driving pressure (mean arterial pressure) decreased after MDL 17043 administration, this increase in coronary blood flow was associated with a decrease in coronary vascular resistance from 0.78 ± 0.25 to 0.62 ± 0.21 mm Hg/min per ml^{-1} ($p < 0.001$).

The baseline arterial oxygen saturation was 93.8 ± 2.9% and decreased slightly but significantly ($p < 0.02$) to 92.4 ± 3.1% at peak cardiac output. The baseline coronary sinus oxygen saturation was 20.9 ± 4.2% and increased to 25.8 ± 4.1% ($p < 0.001$) at peak cardiac output. Therefore, myocardial oxygen extraction decreased from 78 ± 5 to 72 ± 4% ($p < 0.01$) at peak cardiac output (Fig. 2). Accompanying the substantial increment in coronary blood flow, myocardial oxygen consumption increased slightly, but significantly ($p < 0.01$) from 14.1 ± 4.0 to 15.1 ± 3.8 ml/min (Fig. 3). At the drug dose just below that giving the peak cardiac output response, no change was noted in coronary blood flow (131 ± 31 ml/min, p = NS versus baseline) or myocardial oxygen consumption (14.0 ± 4.0 ml/min, p = NS versus baseline).

Lactate metabolism. The administration of MDL 17043 resulted in an increase in arterial lactate from 11.3 ± 4.6

Table 2. Systemic Hemodynamic Response to MDL 17043 in 13 Patients

Case	Optimal Dose (mg/kg)	Peak CI (liters/min per m^2)	HR (beats/min)	Pressure (mm Hg)					
				PCWP	PASP	RAP	SAP	DAP	MAP
1									
Pre		1.5	69	15	40	0	140	50	68
Post	1.5	2.5	69	4	25	0	140	40	60
2									
Pre		1.8	68	30	46	19	130	78	90
Post	1.0	2.3	74	27	44	15	120	67	82
3									
Pre		2.0	80	34	58	14	130	78	86
Post	2.5	2.8	90	25	47	4	112	64	80
4									
Pre		2.1	78	5	18	5	130	78	95
Post	1.5	2.5	104	3	13	7	122	80	82
5									
Pre		2.2	96	30	45	11	90	60	74
Post	1.5	2.3	96	29	47	8	90	64	74
6									
Pre		2.8	96	27	57	8	110	68	84
Post	2.0	3.3	96	16	45	6	103	60	77
7									
Pre		1.3	80	39	75	11	150	95	107
Post	2.5	1.6	90	28	75	10	145	80	104
8									
Pre		1.6	70	25	68	11	135	78	99
Post	1.5	1.9	68	13	43	6	130	68	86
9									
Pre		1.3	110	40	60	16	105	66	79
Post	1.0	2.2	114	23	43	7	105	60	77
10									
Pre		1.6	80	27	57	9	130	66	92
Post	2.0	2.3	80	22	48	3	135	55	87
11									
Pre		1.7	115	14	30	8	104	64	80
Post	1.0	2.7	113	8	23	8	105	54	69
12									
Pre		3.0	84	18	45	9	134	58	77
Post	1.0	3.9	84	16	40	8	115	50	65
13									
Pre		2.4	87	20	50	5	96	65	75
Post	2.5	3.4	96	12	40	4	90	55	67
Mean ± SD									
Pre		1.9 ± 0.5	86 ± 15	25 ± 10	49 ± 15	10 ± 5	122 ± 19	70 ± 12	85 ± 11
Post	1.7 ± 6	2.6 ± 0.6	90 ± 15	17 ± 9	41 ± 15	7 ± 4	116 ± 18	61 ± 11	78 ± 11
p Value		<0.001	<0.05	<0.05	<0.01	<0.05	<0.01	<0.01	<0.05

CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; MAP = mean arterial pressure; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure; Post = after MDL 17043; Pre = before MDL 17043; RAP = right atrial pressure; SAP = systolic arterial pressure.

to 13.8 ± 5.7 mg/dl ($p < 0.02$) and in coronary sinus lactate from 8.8 ± 4.6 to 12.8 ± 6.0 mg/dl ($p < 0.01$). Myocardial lactate extraction was 24 ± 4% in the basal state, and decreased after MDL 17043 administration to 9 ± 5% ($p < 0.05$) (Fig. 4). Three patients developed myocardial lactate production (that is, venous lactate greater than arterial lactate) at the peak drug effect. Additional doses in these patients resulted in further lactate production and a decrease in cardiac output with no change or an increase in left ventricular filling pressure. Two of these patients had ischemic cardiomyopathy and one had idiopathic congestive cardiomyopathy. Lactate extraction was not altered at the dose of MDL 17043 just below that which resulted in the peak cardiac output response (19.2 ± 15%, p = NS versus baseline).

Clinical status. Figure 5 illustrates the clinical status of the study group over a 24 week period as measured by the New York Heart Association functional classification. Twelve

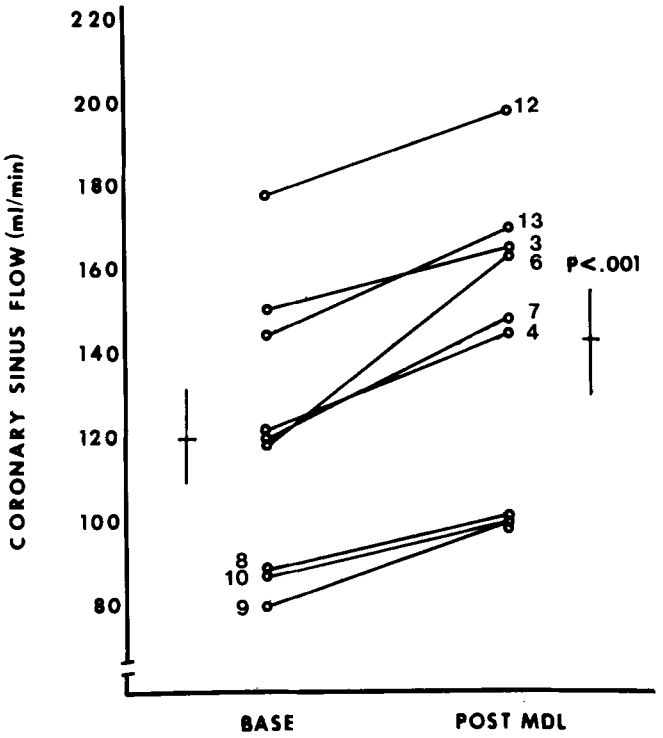


Figure 1. Coronary sinus flow in the basal state (BASE) and at the peak cardiac output response to MDL 17043 (POST MDL). The administration of MDL 17043 was associated with a significant increase in coronary sinus flow from 122 ± 33 to 144 ± 35 ml/min. Individual patients are denoted by number. All patients responded in a similar fashion.

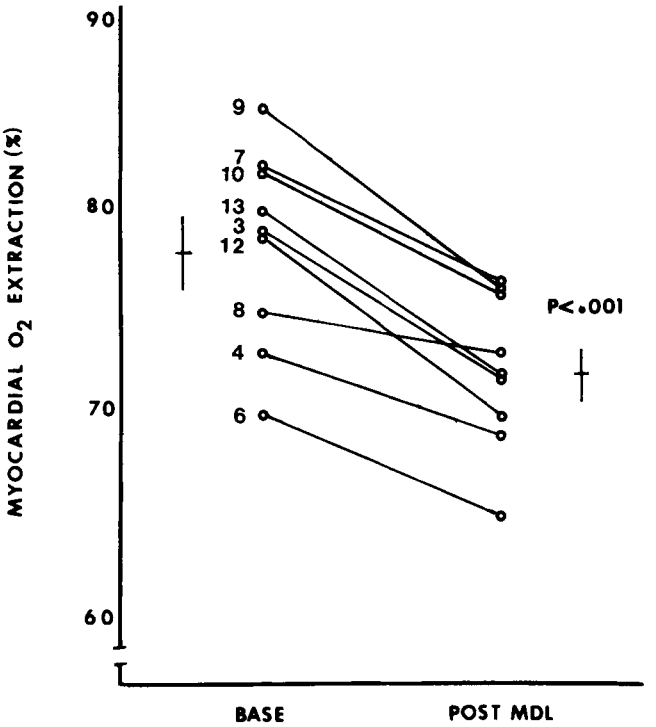
of the 13 patients were taking oral MDL 17043 at a mean dose of 1.5 ± 0.45 mg/kg every 8 hours. Patient 3 developed ventricular tachycardia at the end of the hemodynamic study and was not in the long-term study group. Subsequent electrophysiologic studies with this patient not taking MDL 17043 suggested that the tachycardia may have been unrelated to the drug. Sustained ventricular tachycardia was reproducibly initiated by programmed stimulation with double extrastimuli from the right ventricular apex and outflow tract.

After 2 weeks of therapy, 9 of the 12 patients had improvement of at least one functional class. By 4 weeks of MDL 17043 treatment, four patients were in functional class II and five were in class III; six patients had a reduction in their concomitant diuretic dosage. The initial clinical improvement was sustained in the majority of patients until approximately 8 weeks of therapy, at which point there was a gradual deterioration in the symptomatic status of five of the patients. The deterioration may have been related to drug tolerance or progression of the underlying disease. However, new information became available suggesting that the bioavailability of oral MDL 17043 is between 30 and 60% (personal communications, Merrell Dow Pharmacueticals, Inc.). Accordingly, the MDL 17043 dose was increased from approximately 1.5 mg/kg every 8 hours to 3.0 mg/kg per dose. Several patients responded to this dose increase with a return to their previously attained higher functional class. Thus, 5 of 12 patients had a sustained improvement in clinical status after 20 weeks of therapy. This improvement was maintained at week 24 in three of these five patients (Fig. 5).

Three patients derived little benefit from long-term oral MDL 17043 therapy. Each of these patients was found to have myocardial lactate production during the short-term administration of the drug. One patient died in cardiogenic shock 1 week after the start of treatment with the oral preparation. The remaining two patients were discharged from the hospital, but continued to be severely debilitated; oral MDL 17043 therapy was continued in both, one of whom died 2 days later.

The mean duration of treatment for the entire patient group was 24.1 ± 12.9 weeks. Three patients died suddenly at weeks 17, 24 and 27; four patients died with complications of severe heart failure at weeks 1, 8, 11 and 33. The death at week 11 occurred when the patient was not taking MDL 17043. One patient withdrew from therapy after 16 weeks of treatment because he believed the experimental drug was not helping him; he remains alive but is in functional class IV.

Figure 2. Myocardial oxygen extraction in the basal state and at the peak cardiac output response to MDL 17043. The administration of MDL 17043 was associated with a significant decrease in myocardial oxygen extraction from 78 ± 5 to 72 ± 4%. Individual patients are denoted by number. All patients responded in a similar fashion.



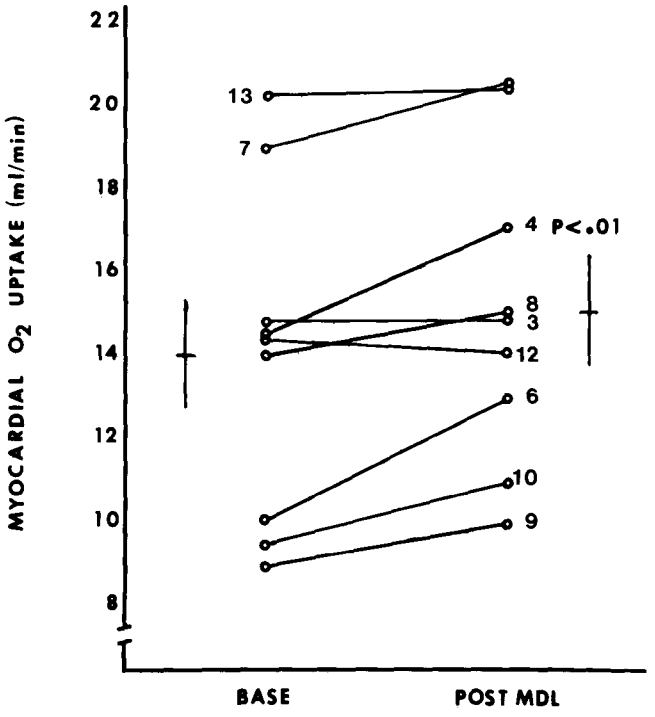


Figure 3. Myocardial oxygen uptake in the basal state and at the peak cardiac output response to MDL 17043. The administration of MDL 17043 was associated with a significant increase in myocardial oxygen uptake from 14.1 ± 4.0 to 15.1 ± 3.8 ml/min. Individual patients are denoted by number.

Side effects. In general, the drug was well tolerated at the doses used in this study. Side effects included leukocytosis (four patients) without evidence of local or systemic infection. Two patients developed moderate hyperglycemia, one of whom required insulin therapy. Two patients developed headache that responded easily to an occasional mild analgesic; one patient complained of frequent bowel movements that were not described as diarrhea. Four patients noted an excessive appetite that was out of proportion to their clinical improvement. None of the patients experienced anginal chest pain.

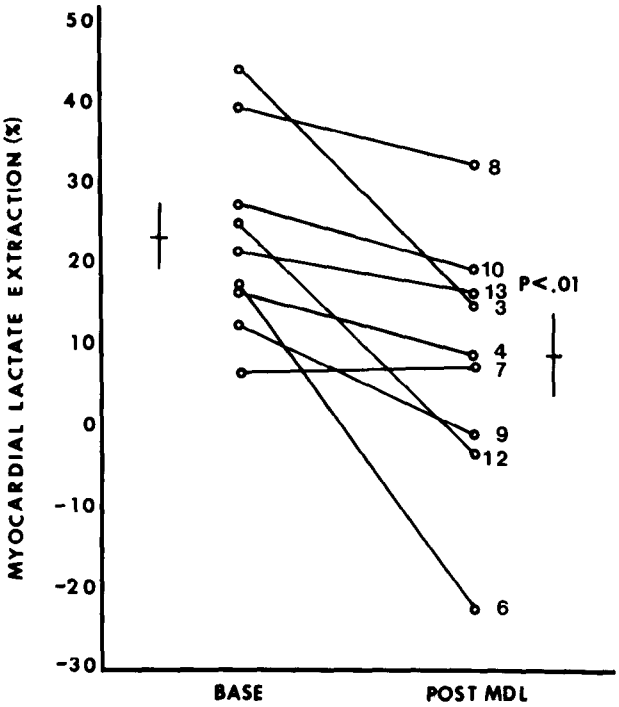
Discussion

MDL 17043 is an intravenous and oral agent that may be useful in the short- and long-term treatment of patients with congestive heart failure (2,5). This agent has been shown to have both inotropic and systemic vasodilatory properties (2–4). Both of these effects would serve to increase the output of the failing left ventricle (10,11). However, both the inotropic and vasodilatory properties could cause myocardial ischemic and, thus, result in a paradoxical reduction in left ventricular function (12,13).

Systemic hemodynamic effects. In the present study, the administration of 1.0 to 2.5 mg/kg of MDL 17043 increased the cardiac index in patients with severe congestive heart failure and a depressed cardiac output at rest. These findings are consistent with studies in animal models (2) of congestive heart failure that have shown a peak increase in cardiac output with 1 mg/kg of MDL 17043 and more chronotropic effects with little, if any, additional inotropic effects at higher doses. In our study, the drug-induced increase in cardiac index was associated with a substantial decrease in the pulmonary capillary wedge pressure with only minimal changes in arterial pressure and heart rate. Studies in animal models (14) of congestive heart failure have also demonstrated substantial reductions in left atrial pressure with little change in systolic blood pressure after the administration of MDL 17043.

Coronary hemodynamic and metabolic effects. Previous studies (15–17) suggest that myocardial ischemia may contribute to left ventricular dysfunction in congestive cardiomyopathy even in the presence of normal coronary arteries. The increased ventricular wall stress in such patients increases oxygen demand (18,19), whereas the increased muscle mass and filling pressures may decrease coronary flow and coronary vascular reserve, particularly in the subendocardium (17,20–22). Thus, agents that interfere with the distribution of available coronary flow or that increase oxygen demand by altering contractility could

Figure 4. Myocardial lactate extraction in the basal state and at the peak cardiac output response to MDL 17043. The administration of MDL 17043 was associated with a significant decrease in myocardial lactate extraction from 24 ± 4 to 9 ± 5%. Three patients (Cases 6, 9 and 12) developed myocardial lactate production (negative lactate extraction) after the administration of MDL 17043. Individual patients are denoted by number.



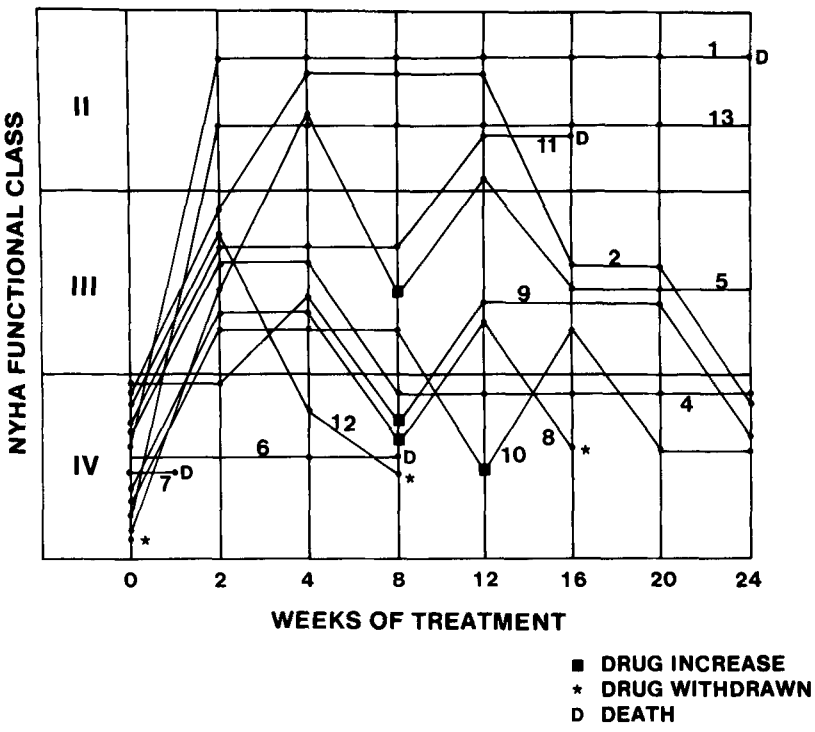


Figure 5. Clinical responses to treatment with oral MDL 17043 as assessed by New York Heart Association (NYHA) functional class. Individual patients are denoted by number. Nine of the 12 patients given oral therapy had an initial improvement of at least one functional class after 2 weeks. The initial clinical improvement was sustained in those patients until 8 weeks, when there was a gradual deterioration in the functional status of five of these patients. An increase in the dose in four patients after week 8 of treatment resulted in an initial favorable response with a return to the previously attained higher functional class. However, this response was transient. Thus, for the group as a whole at weeks 20 and 24, improvement was maintained in a total of five (Cases 1, 2, 5, 9 and 13) and three (Cases 1, 5 and 13) patients, respectively.

potentiate the development of myocardial ischemia in the failing left ventricle. The net result of such compounds on the myocardial oxygen supply-demand relation will, therefore, depend on their ability to reduce systolic wall stress by reducing left ventricular filling pressure and chamber size.

The peak systemic hemodynamic response to MDL 17043 in our study patients was associated with a modest increase in coronary blood flow and myocardial oxygen consumption. A similar increase in coronary blood flow has been observed (2) in dogs after the administration of MDL 17043. Despite the increase in coronary blood flow in our study, a significant decrease occurred in myocardial lactate extraction with three patients developing myocardial lactate extraction with three patients developing myocardial lactate production. It is important to note that the increase in myocardial oxygen demand and decrease in lactate extraction were associated with a substantial decrease in myocardial oxygen extraction. This decrease in oxygen extraction suggests inappropriate shunting of blood flow within the myocardium and may be caused by vasodilatory effects of MDL 17043 on the coronary circulation. It has been suggested (13) that other vasodilating agents may result in intracoronary shunting and potentiate the development of myocardial ischemia in patients with heart failure. The onset of lactate production in some of our patients could be due to a maldistribution of coronary flow or to a modest increase in oxygen demand in the face of a limited supply. Lower doses of MDL 17043 did not alter coronary blood flow of result in lactate production. Thus, our data suggest that lower doses of MDL 17043 may be necessary to avoid these potential deleterious coronary hemodynamic effects.

Comparison with previous studies in human subjects. A previous study by Uretsky et al. (5) reported more dramatic changes in blood pressure and cardiac output after the intravenous administration of MDL 17043 in patients with congestive heart failure. However, in their study substantially higher doses of MDL 17043 were administered. Whether these higher doses would improve myocardial efficiency (cardiac work relative to oxygen utilization) is unknown because coronary hemodynamics and myocardial metabolism were not evaluated. As noted before, our findings suggest that lower doses may be required to avoid the production of myocardial anaerobiosis. Although most of the patients in our study had ischemic cardiomyopathy, patients with idiopathic congestive cardiomyopathy may also have a decreased coronary reserve (17,20–22) and, therefore, might be susceptible to developing myocardial ischemia with large doses of the cardiotonic agent, MDL 17043. Of note is that one of our patients who developed myocardial lactate production had idiopathic congestive cardiomyopathy.

Arterial oxygenation. The administration of MDL 17043 was associated with a slight but significant (93.8 ± 2.9 to 92.4 ± 3.1%) decrease in the arterial hemoglobin oxygen saturation. This occurred despite a decrease in the pulmonary capillary wedge pressure. Thus, it is unlikely that worsening pulmonary vascular congestion accounted for the change in systemic oxygenation. Another potential explanation is ventilation-perfusion mismatching secondary to nonspecific vasodilation in the pulmonary vascular bed. Similar de-

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creases in systemic oxygenation have been reported (23) with other vasodilating agents such as nitroprusside.

Arterial lactate concentration. After the administration of MDL 17043, there was a significant increase in arterial lactate concentration. This may be attributable to one or more mechanisms. As a phophosdiesterase inhibitor, MDL 17043 could increase glycoloysis and thus increase systemic lactate production (24). In addition, peripheral nutritive flow may have deteriorated because of shunting of blood consequent to nonspecific vasodilation (25). Nevertheless, myocardial lactate production is still a valid index of myocardial anaerobiosis in these patients. During exercise in normal subjects, systemic lactate concentration also increases, but myocardial lactate production does not occur (26).

Clinical response. An increase in cardiac output at rest with a cardiotonic agent does not necessarily imply an improvement in effort tolerance and aerobic capacity (8). This is particularly true if there is a potential for the development of ischemic left ventricular dysfunction during exercise. Moreover, if a nonspecific vasodilator is administered then generalized vasodilation may result in functional shunting to less metabolically active tissues. As a result, the increased cardiac output may not result in increased oxygen delivery to working skeletal muscle during physical activity (25).

Our study included patients with severe decompensated congestive heart failure. We were unable, therefore, to measure their maximal oxygen consumption before the administration MDL 17043. Nonetheless, the acute clinical response to oral therapy with this agent was favorable. Most patients had an increase in their subjective exercise tolerance as reflected in an improvement of at least one functional class. This improvement occurred with no other change in their medical regimen of, in some cases, with a decrease in concomitant medications (for example, diuretic drugs). The maintenance of this favorable response beyond 8 to 12 weeks required an increase in the oral dose of MDL 17043 in some patients. The failure of most patients to maintain a beneficial response at 24 weeks may be due to drug tolerance, progression of their underlying disease or adverse coronary hemodynamic effects. Further study is necessary to answer this question.

Clinical implications. MDL 17043 is an orally effective inotropic and vasodilator agent. Therefore, it may be useful in the short- and long-term treatment of patients with advanced congestive heart failure. However, the peak cardiac output response to the administration of this agent may be associated with an increase in myocardial oxygen demand and may produce intracoronary shunting of blood flow consequent to vascular smooth muscle dilation. These effects may result in myocardial anaerobiosis in selected patients. Thus, to obtain an optimal response in myocardial energics to MDL 17043, it may be necessary to administer doses that result in only moderate increases in the cardiac output. Additional studies with individual dose titration and hemodynamic monitoring will be necessary to further assess the value of this agent in the management of patients with congestive heart failure.

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