

Myocardial energetics and efficiency in patients with idiopathic cardiomyopathy: Response to dobutamine and amrinone

Nine consecutive patients having severe idiopathic dilated cardiomyopathy were studied for their response in ventricular function, coronary sinus blood flow and myocardial oxygen consumption, lactate extraction and efficiency following incremental doses of dobutamine, followed by the combination of dobutamine and the phosphodiesterase inhibitor amrinone. Results, presented as baseline and the response to the peak dose (15 $\mu\text{g}/\text{kg}/\text{min}$) of dobutamine and to the combination of dobutamine and amrinone (each at 15 $\mu\text{g}/\text{kg}/\text{min}$) (differences compared with baseline) were: wedge pressure decreased from 28 ± 7 to 26 ± 8 mm Hg ($p = \text{NS}$) and to 20 ± 6 mm Hg ($p < 0.01$); cardiac index rose from 1.47 ± 0.44 L/min/m² to 2.89 ± 1.1 L/min/m² ($p < 0.01$) and to 3.64 ± 1.05 L/min/m² ($p < 0.001$); myocardial oxygen consumption remained invariant (18 ± 8 , 17 ± 5 , and 19 ± 5 ml/min) despite progressive increments in minute work from 2.96 ± 1.1 to 6.98 ± 3.9 kg - m/min ($p < 0.01$) and to 9.38 ± 4.3 kg - m/min ($p < 0.001$); myocardial lactate extraction rose from $21 \pm 10\%$ to $30 \pm 15\%$ ($p = \text{NS}$) and to $35 \pm 10\%$ with the addition of amrinone ($p < 0.01$). No patient had net lactate efflux into the coronary sinus, and myocardial efficiency improved from $9.5 \pm 5\%$ to $21.7 \pm 13.0\%$ ($p < 0.01$) and to $28.0 \pm 18.0\%$ ($p < 0.01$). Thus in idiopathic dilated cardiomyopathy, dobutamine and the combination of dobutamine and amrinone have additive beneficial effects on ventricular performance without an adverse elevation in myocardial oxygen consumption or lactate production, resulting in improved efficiency, suggesting the presence of significant metabolic reserve within the failing myocardium. (AM HEART J 1990;119:891.)

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One of the major objectives in the management of patients with advanced chronic cardiac failure is a drug-mediated improvement in ventricular function. A considerable experience with pharmacologic agents that have both vasoactive and inotropic properties has emerged in these patients. Salutary hemodynamic effects have been observed, indicating in part that the contractility of the failing myocardium can be augmented with pharmacologic doses of β -agonists, like dobutamine,^{1,2} or phosphodiesterase inhibitors, such as amrinone.^{3,4} In raising contractility, however, dobutamine may adversely elevate myocardial oxygen consumption in the presence of coronary artery disease and cause myocardial anaerobiosis.⁵ Previous studies⁶⁻⁹ with various phosphodiesterase

inhibitors have not shown a similar adverse result. In either case, however, effective therapeutic strategies with such agents should be designed to improve myocardial efficiency (i.e., the relative energy cost of performing useful work).

At present, it is unclear whether a combination of these agents, acting by different mechanisms of action to improve the performance of the severely failing myocardium, would adversely affect myocardial oxygen availability as ventricular work is augmented. In addition, while myocardial lactate production is a real concern in the setting of coronary artery disease, it is unclear whether patients with idiopathic dilated cardiomyopathy are at similar risk with the combined use of these agents. Accordingly, this study was undertaken. Its purpose was to examine myocardial energetics and efficiency in patients with idiopathic dilated cardiomyopathy during incremental dosing with dobutamine alone and with dobutamine in combination with amrinone. To this end, we monitored ventricular work, myocardial oxygen utilization, and lactate extraction at the bedside in our cardiac care unit.

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METHODS

Study population. Nine consecutive patients (all males) referred to this hospital for treatment of severe congestive heart failure secondary to advanced idiopathic dilated cardiomyopathy were enrolled in the study. Mean age was 55 years, ranging from 29 to 69 years. All patients had previously undergone contrast ventriculography and coronary angiography documenting the absence of significant coronary artery obstruction. The presence of severe dilated cardiomyopathy was further confirmed by combined M-mode and two-dimensional echocardiography. All drugs were withheld on the day of the study, with vasodilators being discontinued for at least 24 hours prior to the initiation of the study. Informed consent, previously approved by the Institutional Review Board of this hospital, was obtained from all patients.

Invasive monitoring. The study was conducted at the bedside in the cardiac care unit. Under continuous electrocardiographic monitoring and under fluoroscopic guidance, a Baim thermodilution coronary sinus catheter (Elecath, Rahway, N.J.) was positioned in the coronary sinus and the tip was advanced to the great cardiac vein, such that the proximal thermistor would measure coronary sinus blood flow and the distal thermistor would measure great cardiac vein blood flow. Accurate positioning of this catheter was confirmed by small injections of Renografin-76 (E.R. Squibb & Sons, Inc., New Brunswick, N.J.). To ensure that right atrial reflux did not interfere with thermodilution measurements, the following precautions were taken: (1) the tip of the catheter was placed well into the great cardiac vein, such that the proximal thermistor and sampling port were at least 2 to 3 cm beyond the coronary sinus ostium; (2) injections of cold 5% dextrose in water into the right atrium for cardiac output measurements did not cause any voltage deflections from the proximal coronary sinus thermistor; (3) intermittent comparisons were made between the coronary sinus and great cardiac vein oxygen saturations to ensure that they were similar; and (4) repeat fluoroscopy was performed intermittently throughout the procedure with the bedside C-arm, and at the end of the procedure to ensure that catheter position was stable. Repeat determinations of coronary sinus blood flows were measured by the continuous thermodilution technique¹⁰⁻¹² using a Baim coronary sinus flow analyzer (Elecath) coupled with a flow calculator. An average of two to three readings were taken, ensuring that there was less than 10% variation between individual readings. Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were monitored using a standard fluoroscopically positioned flotation catheter, which was also used for thermodilution cardiac output measurements. Arterial pressure was monitored continuously using a 20-gauge radial arterial cannula. All pressures were measured at end-expiratory with the patient in the supine or semirecumbent position with appropriately positioned transducers. Arterial and coronary sinus blood samples were analyzed for oxygen saturation by standard oximetric techniques using an OSM-2 Hemoximeter (Radiometer A/S, Copenhagen, Denmark) at the bedside. Coronary sinus and systemic arterial

lactate levels were also determined at the bedside by a rapidly responding lactate analyzer (YSI Model 23L, Yellow Springs Instrument Co., Inc., Yellow Springs, Ohio). At least three separate determinations of oxygen saturations and lactate measurements were made on each sample, ensuring that values were near identical.

The following parameters were measured at each data collection point: heart rate; systemic arterial, right atrial, pulmonary arterial, and pulmonary capillary wedge pressures; cardiac output; systemic and coronary sinus oxygen saturations; systemic and coronary sinus lactate concentration; and coronary sinus and great cardiac vein blood flows. Derived variables were calculated as follows: $MEP = 0.8 \times (SBP - DBP) + DBP$, where MEP, SBP, and DBP are mean ejection, systolic, and diastolic blood pressures, respectively, measured in millimeters of mercury; $SV = CO/HR$, where SV is stroke volume in milliliters, CO is cardiac output in liters per minute, and HR is heart rate in beats per minute; $SW = (MEP - PCW) \times SV \times 0.0136$, where SW is stroke work in gram meters and PCW is pulmonary capillary wedge pressure in millimeters of mercury; $MW = SW \times HR$, where MW is minute work in gram meters per minute; $Myocardial\ A-V\ O_2\ Diff = Art\ O_2\ content - Coronary\ Sinus\ O_2\ content$, where A-V O₂ Diff is the O₂ content difference between arterial and coronary sinus blood and the units for arterial (Art O₂) and coronary sinus O₂ content are in milliliters of oxygen per liter; $MVO_2 = Q \times Myocardial\ A-V\ O_2\ Diff$, where MVO₂ is myocardial O₂ consumption in milliliters of oxygen per minute and Q is coronary blood flow in liters per minute; $LEXT = [(L_{Art} - L_{Ven})/L_{Art}] \times 100\%$, where LEXT is percent lactate extraction and L_{Art} and L_{Ven} are arterial and coronary sinus lactate concentrations, respectively in milligrams per deciliter; and $EFF = MW/[MVO_2 \times 2069] \times 100\%$, where EFF is percent myocardial efficiency.

Protocol. Control measurements of hemodynamic and metabolic parameters were made at least 2 hours following any contrast injection and at least 4 hours into the postprandial state. A stable, reproducible baseline was established over 1 hour. Dobutamine was then administered at increasing doses of 5, 10, and 15 $\mu\text{g}/\text{kg}/\text{min}$. All parameters were measured, and derived quantities were calculated at 10 minutes after initiation of each infusion rate. Discontinuation criteria were as follows: (1) a plateau (less than 15% increase) in cardiac output; (2) net coronary sinus lactate efflux; (3) an increase in ventricular premature beats greater than 5/min over baseline; or (4) a rise in systolic blood pressure above 170 mm Hg. However, none of the patients enrolled needed to have the study discontinued because of any of these side effects. Three other patients (i.e., other than the nine patients studied) were not enrolled in the protocol because it was felt that the coronary sinus catheter placement was not ideal, and could therefore have led to erroneous measurements. Following incremental dosing with dobutamine, the dobutamine infusion was continued at 15 $\mu\text{g}/\text{kg}/\text{min}$. A 1 mg/kg loading dose of amrinone was then administered over 5 minutes, followed immediately by a sustaining infusion of amrinone

Table I. Hemodynamic response of the study population to dobutamine and at the peak effect (peak cardiac index) of combined dobutamine and amrinone

Patient no.	Condition	Peak CI (L/min/m ²)	SV (ml)	PCWP (mm Hg)	RAP (mm Hg)	HR (beats/min)	BP (mm Hg)	MW (kg-m/min)
1	Baseline	1.04	24	35	22	79	135/76	2,269
	Dobut 15 µg/kg/min	1.70	31	36	15	98	153/83	3,718
	Dobut & Amrinone	1.87	31	25	10	109	137/68	3,998
2	Baseline	1.38	24	36	27	110	133/84	3,124
	Dobut 15 µg/kg/min	2.83	51	30	15	105	140/75	7,064
	Dobut & Amrinone	4.58	81	18	6	106	132/54	11,444
3	Baseline	1.29	41	28	18	57	112/66	2,384
	Dobut 15 µg/kg/min	2.35	69	28	15	62	119/59	4,596
	Dobut & Amrinone	3.88	84	31	24	84	156/79	10,555
4	Baseline	1.48	29	28	15	101	137/95	4,008
	Dobut 15 µg/kg/min	4.92	76	29	10	129	160/87	15,372
	Dobut & Amrinone	4.71	72	19	10	129	171/84	17,078
5	Baseline	2.36	33	17	2	124	112/55	4,675
	Dobut 15 µg/kg/min	3.23	47	10	1	119	147/66	9,149
	Dobut & Amrinone	4.87	70	4	0	119	149/63	13,482
6	Baseline	1.53	22	24	10	124	101/48	2,449
	Dobut 15 µg/kg/min	2.48	32	15	2	140	127/75	6,215
	Dobut & Amrinone	3.21	39	11	2	150	137/69	8,912
7	Baseline	1.15	18	34	20	114	103/74	1,758
	Dobut 15 µg/kg/min	2.64	44	28	13	106	110/70	4,694
	Dobut & Amrinone	3.51	55	25	10	112	120/65	7,100
8	Baseline	1.06	17	33	20	114	104/75	1,713
	Dobut 15 µg/kg/min	1.63	24	31	11	123	112/67	2,891
	Dobut & Amrinone	2.28	35	18	5	118	110/47	4,437
9	Baseline	1.97	38	21	12	97	91/54	4,211
	Dobut 15 µg/kg/min	4.25	65	26	9	121	93/51	9,075
	Dobut & Amrinone	3.84	59	16	8	120	84/77	7,414

BP, Blood pressure; CI, cardiac index; HR, heart rate; MW, minute work; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SV, stroke volume; Dobut, dobutamine.

at 15 µg/kg/min. Measurements were taken 15 minutes after this combination of amrinone at 15 µg/kg/min and of dobutamine at 15 µg/kg/min. If the cardiac output changed by less than 15%, a second loading dose of amrinone (1.5 mg/kg) was administered and measurements were taken 15 minutes after continuation of the maintenance infusions of dobutamine and amrinone mentioned above.

Statistical analysis. The hemodynamic and metabolic parameters measured were subjected to an analysis of variance with repeated measures to determine overall drug effects. Comparisons using paired *t* tests were then made between baseline and drug effects at each dose of dobutamine and the peak effect of the combination of dobutamine and amrinone. Results are presented as mean ± 1 standard deviation, and differences were considered significant at *p* values of less than 0.05 after adjustment by the Bonferroni method.

RESULTS

Hemodynamics. Table I lists for each patient the baseline hemodynamic profile alone, the profile obtained in response to dobutamine, and the profile obtained with the combination of dobutamine and amrinone. Cardiac index rose from 1.47 ± 0.44 L/min/m² at baseline to 2.89 ± 1.1 L/min/m² (*p* < 0.01)

with the peak dose of dobutamine, and to a peak value of 3.64 ± 1.05 L/min/m² with the addition of amrinone (*p* < 0.001 versus baseline and *p* < 0.05 versus dobutamine). Pulmonary wedge pressure did not change from baseline (28 ± 7 mm Hg) with the peak dose of dobutamine but did increase significantly to 20 ± 6 mm Hg with the addition of amrinone (*p* < 0.01 versus baseline and *p* < 0.05 compared with dobutamine). Right atrial pressure decreased from 16 ± 7 mm Hg at baseline to 10 ± 5 mm Hg with the peak dose of dobutamine (*p* < 0.001), and to 8 ± 7 mm Hg with the addition of amrinone (*p* < 0.01 versus baseline and *p* = NS versus dobutamine). Heart rate increased but did not reach the level of statistical significance from the baseline value of 102 ± 22 beats/min following the peak dose of dobutamine, while the increase to 116 ± 18 beats/min with the addition of amrinone was significant (*p* < 0.05 versus baseline). Minute work increased from 2.96 ± 1.1 kg-m/min at baseline to 6.98 ± 3.9 kg-m/min with the peak dose of dobutamine (*p* < 0.01), and to 9.38 ± 4.3 kg-m/min with the addition of amrinone (*p* < 0.001 versus baseline and

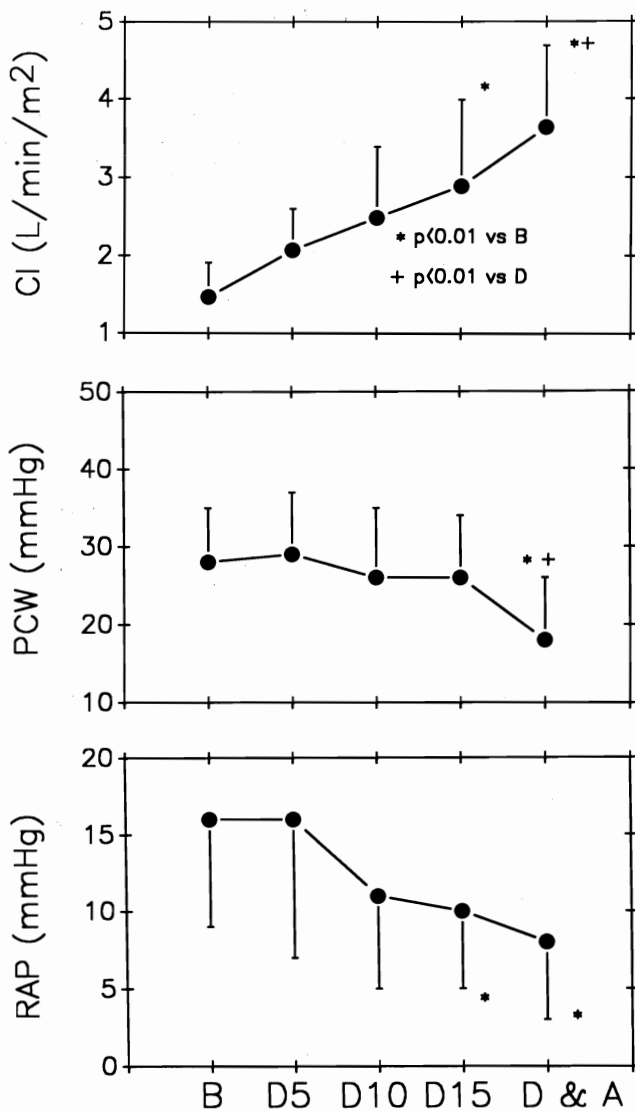


Fig. 1. Cardiac index (CI), pulmonary capillary wedge pressure (PCW), and right atrial pressure (RAP), at baseline (B) and in response to incremental doses of dobutamine (D) at 5, 10, and 15 $\mu\text{g}/\text{kg}/\text{min}$ and the peak effect of the combination of dobutamine and amrinone (D & A).

$p < 0.05$ versus dobutamine). Fig. 1 illustrates the cardiac index, right atrial pressure, and pulmonary wedge pressure responses during the study. Fig. 2 illustrates the response in heart rate during the study; in Fig. 3, the response in minute work is presented.

Coronary flow, myocardial metabolism, and efficiency. Table II lists coronary sinus blood flow and myocardial oxygen consumption, efficiency, and lactate extraction in individual patients at baseline, and in response to the peak dose (15 $\mu\text{g}/\text{kg}/\text{min}$) of dobutamine and during the combined infusion of the combination of dobutamine and amrinone. Figs. 3

and 4 illustrates these changes for the study population.

There was no significant change in coronary blood flow for the patients during the course of this study. Averaged flows were 128 ± 61 , 113 ± 43 , 133 ± 53 , and 120 ± 37 ml/min at baseline and with 5, 10, and 15 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine, respectively. The addition of amrinone did not significantly change coronary blood flow (137 ± 41 ml/min). It should be noted that patient No. 7 needed repositioning of the coronary sinus catheter (only during dobutamine infusion). However, statistical analysis of the patient group excluding this patient did not make any significant difference to the results. Changes in myocardial oxygen consumption were statistically insignificant: 18 ± 8 , 16 ± 6 , 19 ± 7 , 17 ± 5 , and 19 ± 5 ml/min for baseline, dobutamine at 5, 10, and 15 $\mu\text{g}/\text{kg}/\text{min}$, and with the combination of dobutamine and amrinone, respectively.

Myocardial efficiency improved from a baseline value of $9.5 \pm 5\%$ to $21.7 \pm 13\%$ with the peak dose of dobutamine ($p < 0.01$) and to $28 \pm 18\%$ with the addition of amrinone ($p < 0.01$ versus baseline and $p = \text{NS}$ versus dobutamine). Lactate extraction improved from a baseline of $21.4 \pm 10\%$ to $38 \pm 18\%$ with 5 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine ($p < 0.05$), remained statistically unchanged from baseline ($30.3 \pm 15\%$) with 15 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine, but then rose again to $34.9 \pm 10\%$ with the addition of amrinone ($p < 0.01$ compared with baseline and $p = \text{NS}$ compared with any dose of dobutamine).

DISCUSSION

The safe use of any therapeutic agent having inotropic or vasodilator properties, or both, in patients with severe cardiac (myocardial) failure mandates an understanding of its influence on mechanics and energetics of the failing ventricle and thereby on myocardial efficiency. Patients with idiopathic dilated cardiomyopathy have elevated myocardial oxygen demand because of increased systolic wall stress, or afterload.¹³ Moreover, the absence of coronary artery disease in these patients would not preclude them from an adverse elevation in myocardial oxygen consumption with the use of such pharmacologic agents. Potential increments in oxygen requirements could precipitate myocardial anaerobiosis and worsen underlying myocardial dysfunction¹⁴ and promote ventricular arrhythmias.

The determinants of myocardial oxygen consumption¹⁵ and the concept of the heart's metabolic reserve,^{16,17} defined as the reserve in oxygen availability that will accommodate increments in ventricular work without lactate production, are useful in

Table II. Baseline and peak responses in energetics, lactate extraction, and efficiency to dobutamine and combined dobutamine and amrinone

Patient no.	Condition	CBF (ml/min)	MVO ₂ (ml O ₂ /min)	Efficiency (%)	Lac Ext (%)
1	Baseline	212	30.5	4	25
	Dobut 15 µg/kg/min	116	16.6	11	29
	Dobut & Amrinone	148	20.7	9	45
2	Baseline	73	11.2	13	31
	Dobutamine 15 µg/kg/min	65	10.6	32	39
	Dobutamine & Amrinone	64	9.5	59	35
3	Baseline	78	9.9	12	1
	Dobut 15 µg/kg/min	87	10.7	21	18
	Dobut & Amrinone	110	15.3	34	31
4	Baseline	61	10.0	19	20
	Dobut 15 µg/kg/min	96	14.5	51	59
	Dobut & Amrinone	111	17.4	48	44
5	Baseline	126	16.1	14	29
	Dobut 15 µg/kg/min	132	16.6	27	29
	Dobut & Amrinone	127	15.6	42	44
6	Baseline	103	17.2	7	33
	Dobut 15 µg/kg/min	130	20.3	15	39
	Dobut & Amrinone	145	20.8	21	33
7	Baseline	212	25.3	3	21
	Dobut 15 µg/kg/min	127	16.4	14	15
	Dobut & Amrinone	204	26.3	13	23
8	Baseline	100	14.2	6	13
	Dobut 15 µg/kg/min	135	17.7	8	12
	Dobut & Amrinone	152	19.2	11	16
9	Baseline	189	26.5	8	20
	Dobut 15 µg/kg/min	194	26.8	16	33
	Dobut & Amrinone	175	23.9	15	43

CBF, Coronary blood flow; Lac Ext, lactate extraction; MVO₂, myocardial oxygen consumption; Dobut, dobutamine.

understanding the physiologic consequences of inotropic or vasodilator therapy in these patients. Myocardial oxygen consumption is primarily determined by heart rate, contractility, and systolic wall stress.^{15, 17} The overall response in myocardial oxygen consumption to positive inotropic agents will depend on the opposing effects that these agents may have on these determinants of oxygen utilization. In the enlarged, failing heart, these agents may raise contractility but at the same time reduce chamber size and therefore systolic wall stress. The net result is no change in myocardial oxygen uptake. In addition, by reducing ventricular filling pressure, these agents improve subendocardial perfusion. It is therefore difficult to predict the net change in oxygen uptake with these agents using simple indices of ventricular work alone. This becomes even more difficult when a combination of inotropic agents is used. Thus it is necessary to measure myocardial energetics in such situations and to calculate the response in myocardial efficiency directly.

Under conditions where both oxygen extraction and coronary vasodilation are physiologically maxi-

mum, the metabolic reserve of the heart is fully utilized. Any further demand for oxidative metabolism cannot be accommodated. This state has been viewed as the aerobic limit of the heart.¹⁶ Further increments in ventricular work result in cellular hypoxia with lactate production. In the isolated canine heart, ventricular performance falls quickly and pulsus alternans appears with the onset of anaerobic metabolism.^{16, 18} Myocardial anaerobiosis should therefore be avoided in man and, when present in response to inotropic agents, would be expected to impair ventricular pump function.

The energy costs of combined dobutamine and amrinone therapy are unknown in patients with idiopathic dilated cardiomyopathy. Dobutamine, a β -agonist, given alone is known to increase contractility and in some patients with coronary artery disease may increase myocardial oxygen consumption and cause myocardial lactate production.⁵ Amrinone is known to improve ventricular function due to a combination of augmented contractility and systemic vasodilation.^{3, 19} It has not been shown to raise myocardial oxygen uptake, but did cause myocardial

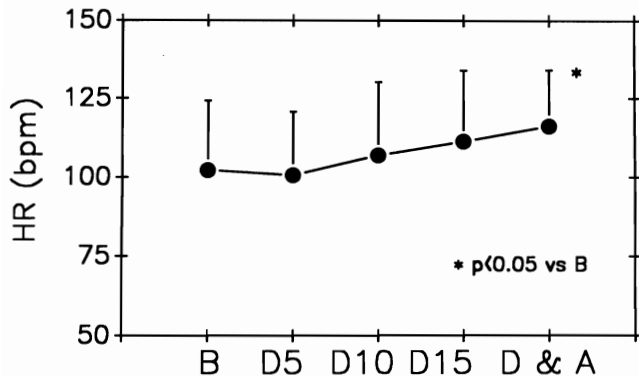


Fig. 2. Heart rate (*HR*) at baseline (*B*) and in response to incremental doses of dobutamine at 5, 10, and 15 $\mu\text{g/kg/min}$ (*D5*, *D10*, and *D15*) and at the peak effect of the combination of dobutamine and amrinone (*D & A*).

lactate production in some patients with coronary artery disease.⁴ Other phosphodiesterase inhibitors like milrinone and enoximone (MDL 17,043) have also been shown to have salutary hemodynamic effects without raising myocardial oxygen uptake.⁶⁻⁹ Gage et al.²⁰ have recently reported the additive effects of dobutamine and amrinone on the first derivative of left ventricular pressure and ventricular performance in a group of patients with ischemic and nonischemic heart failure; myocardial energetics, however, were not evaluated.

Hemodynamic response. Our study demonstrates that dobutamine administration resulted in a significant increase in cardiac output and minute work and a concomitant decrease in right ventricular filling pressure. Wedge pressure, however, remained unchanged. All patients received our maximal dobutamine dose (15 $\mu\text{g/kg/min}$) prior to the addition of amrinone. The addition of amrinone resulted in a further increase in cardiac index in all patients except patients No. 4 and 9, and a large increase in minute work in all patients except patient No. 9. In patients No. 4 and 9 the decline in left ventricular filling pressure that accompanied the administration of amrinone may have been to a level less than the ideal filling pressure for the ventricle, hence attenuating the salutary hemodynamic response to amrinone. Alternatively, the ventricle may have been close to its aerobic limit with 15 $\mu\text{g/kg/min}$ of dobutamine, and further inotropic therapy may have been ineffectual. Neither of these patients developed pulsus alternans. Our findings confirm that the continued use of a β -agonist and the addition of a phosphodiesterase inhibitor have an additive effect on ventricular function. In addition, the downregulation of β -receptors that occurs in such patients^{21,22} makes it

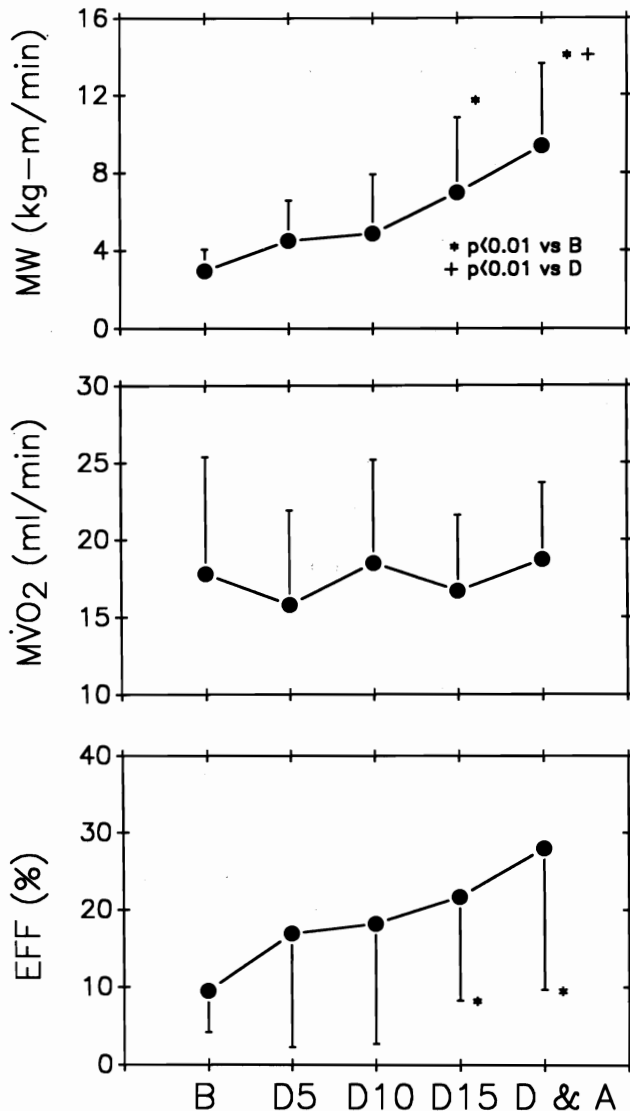


Fig. 3. Minute work (*MW*), myocardial oxygen consumption (*MVO₂*) and efficiency (*EFF*) at baseline (*B*) and in response to incremental doses of dobutamine at 5, 10, and 15 $\mu\text{g/kg/min}$ (*D5*, *D10*, and *D15*) and at the peak effect of the combination of dobutamine and amrinone (*D & A*).

conceptually attractive that an agent like amrinone, which does not utilize β -receptors, could have an additive effect on an otherwise refractory myocardium.

Myocardial energetics. Myocardial oxygen consumption remained essentially invariant during dobutamine administration alone and following the addition of amrinone, despite large increments in minute work. This in all likelihood reflects the counterbalancing influences of enhanced contractility and reduced systolic wall stress on net myocardial oxygen consumption. With dobutamine, the effects of improved contractility on myocardial oxygen consump-

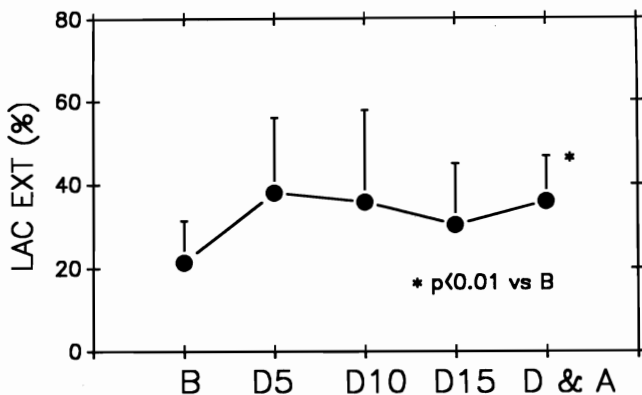


Fig. 4. Lactate extraction (*LAC EXT*) at baseline (*B*) and in response to incremental doses of dobutamine at 5, 10, and 15 µg/kg/min (*D5*, *D10*, and *D15*) and at the peak effect of the combination of dobutamine and amrinone (*D & A*).

tion would be offset by a corresponding fall in left ventricular end-systolic volume, resulting in a reduction in instantaneous systolic wall stress. Similar changes in ventricular volume would also accompany amrinone administration,^{3, 4, 23} both because of its inotropic and vasodilator properties.

Large increases in minute work with relatively invariant myocardial oxygen consumption resulted in a significant increase in left ventricular mechanical efficiency. However, the addition of amrinone did not result in any statistically significant change in efficiency when compared with the peak dose of dobutamine. Myocardial lactate extraction rose insignificantly with the initiation of dobutamine at 5 µg/kg/min, but was statistically unchanged from baseline values at the peak dose of the drug. The addition of amrinone resulted in a significant increase from baseline values, but not when amrinone was compared with dobutamine at any of the three doses. However, lactate extraction actually rose with the addition of amrinone to dobutamine in all patients except patients No. 4 and 9.

The relationship between myocardial ischemia, anaerobic metabolism, and coronary sinus lactate measurements has been studied by several investigators.²⁴⁻²⁶ Their findings indicate that the measurement of coronary sinus lactate is influenced by several factors, including the time course of lactate production and the admixture of venous blood draining areas of ischemic and nonischemic myocardium. This heterogeneity, however, should be of less concern in our patients who did not have coronary artery disease. In view of the heterogeneity of lactate kinetics in the myocardium,²⁶ however, generalized conclusions on lactate extraction ratio and lactate production must be interpreted with caution. In addi-

tion, the recent studies of Gertz et al.²⁵ indicate that positive values of lactate extraction cannot be considered abnormal. None of the patients in our study had overt lactate production, either at baseline or during drug administration. All patients, however, did have low baseline lactate extraction ratios of less than 20%. Five patients had lactate extraction ratios of less than 10%, possibly indicating a tendency towards anaerobic metabolism at baseline. The improvement in lactate extraction with the administration of dobutamine and amrinone, despite large increases in minute work, suggests improved myocardial efficiency.

Potential limitations of our study should be addressed. First, coronary sinus sampling may not completely reflect the energetics of the entire left ventricle, especially because of variations in regional venous drainage within the myocardium and between patients. Comparisons between different patients are therefore difficult. However, we used each patient as his own control. Second, we were only able to measure external work as representing the entire energy expenditure of the left ventricle. It is recognized, however, that there is also a certain energy requirement necessary for the internal work of the myocardium,¹⁵ such as that associated with the chemical activation of the contractile process and the maintenance of the active state. Moreover, heat loss was not measured. Third, acute responses in hemodynamics and myocardial energetics with the initial administration of dobutamine and amrinone may not reflect the long-term response to prolonged administration of these agents.

In conclusion, our study demonstrates that dobutamine and amrinone, acting by different mechanisms of action, have additive beneficial effects on ventricular function in patients with advanced chronic cardiac failure due to idiopathic dilated cardiomyopathy. This additive effect occurs without undue side effects. Safety of such combined administration was confirmed by relatively invariant myocardial oxygen consumption and improved myocardial lactate extraction, despite progressive and large increases in minute work. Improvement in ventricular performance without a corresponding increase in energy expenditure resulted in improved myocardial efficiency. Such a combined hemodynamic/metabolic approach can be safely conducted at the bedside in the cardiac care unit by experienced personnel, and may be of value in the management of selected patients with severe cardiac failure.

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