

Cardiac work and myocardial substrate extraction in congestive cardiomyopathy

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SUMMARY Left ventricular pressure, cardiac output, coronary sinus blood flow, and myocardial substrate extraction were measured in 10 patients with congestive (dilated) cardiomyopathy and in a control group of nine patients investigated for chest pain who proved to have no angiographic or metabolic evidence of ischaemic heart disease. Haemodynamic and angiographic measurements confirmed that the patients with cardiomyopathy had severe left ventricular disease. Coronary sinus blood flow and myocardial oxygen consumption were greater in the patients with cardiomyopathy, but were similar in the two groups when normalised for ventricular mass. Efficiency, estimated from the oxygen cost of external work, was grossly reduced in the cardiomyopathy group. No major differences in substrate extraction were demonstrated between the groups. Myocardial lactate production was not observed in any patient with cardiomyopathy. Free fatty acid and glycerol release were observed in several control subjects but in none of the patients with cardiomyopathy.

Measurements were repeated during pacing in five of the cardiomyopathy group and in each of the control subjects. The latter showed a normal response to pacing, whereas of the former, four sustained increases in end-diastolic pressure, two showed large reductions in both cardiac output and coronary flow, and only one increased coronary flow during pacing. Despite the failure of coronary flow to increase, lactate extraction remained high.

These results show that anaerobic carbohydrate metabolism is not an important energy source for the myopathic heart and suggest that ischaemia does not contribute to poor left ventricular function. No gross abnormality of oxidative metabolism was identified, implying that low efficiency lay in the poor contractile performance of the myopathic heart.

Congestive, or dilated, cardiomyopathy is a descriptive diagnosis attached to those patients with a primary disorder of cardiac muscle which results in ventricular dilatation, little if any hypertrophy, and reduced ejection.^{1,2} Investigation rarely yields the aetiology, and microscopical examination of endomyocardial biopsy specimens usually demonstrates non-specific muscle damage.^{3,4} Microchemical analysis of biopsy material has shown conspicuously raised levels of cytosol lactate dehydrogenase,⁵ though this is not a specific marker for the disease, as moderately increased concentrations are found in patients with poor ventricular function secondary to valvular disease.⁵ The significance of this finding is uncertain, but because there have been occasional reports of myocardial lactate production in congestive car-

diomyopathy^{6,7} it has been suggested that the increased lactate dehydrogenase levels reflect the importance of anaerobic carbohydrate metabolism as an energy source for the myopathic heart.⁵

We have measured haemodynamics, coronary blood flow, and myocardial substrate extraction in 10 patients with severe congestive cardiomyopathy, and in a control group of nine patients investigated for chest pain in whom no cardiac abnormality was found. This study was undertaken to investigate the relation between cardiac work and energy consumption and to identify any abnormality of substrate extraction by the myopathic heart.

Patients and methods

Two groups of patients were studied; 10 patients who had clinical evidence of heart failure thought to result from congestive cardiomyopathy, and nine patients

without heart failure who were under investigation for disabling chest pain. The procedure was approved by the hospital ethical committee, and each patient gave written consent.

All studies were performed in the morning after an overnight fast. Digoxin and diuretics were continued in the cardiomyopathy group until the time of study, but in the chest pain group beta-blocking drugs were stopped 48 hours beforehand. Premedication was with atropine 0.3 mg and diazepam 10 mg intramuscularly. At the same time heparin (45 units/kg) was given intravenously to minimise the effect of a subsequent dose of heparin upon free fatty acid concentrations.⁸ Right and left heart catheterisation was performed via the right femoral vein and artery. Immediately after arterial catheterisation a second dose of heparin (45 units/kg) was administered. After routine pressure measurements and coronary arteriography, a Ganz catheter was advanced into the coronary sinus via a left antecubital vein, and its position confirmed by injection of contrast. Cold saline was injected into the right atrium to ensure that the dilution thermistor was unaffected by reflux of atrial blood.⁹ Using the long sheath technique¹⁰ a catheter tip micromanometer (either a Telco MM52 or No. 5 Millar) was positioned in the body of the left ventricle. In each of the nine patients with chest pain and in four of the patients with cardiomyopathy the retrograde aortic route was used, but in six patients with cardiomyopathy the catheter was positioned transseptally. Cardiac output was measured by dye dilution using a Schwarzer Swan-Ganz catheter positioned in the pulmonary artery, or (in four patients with cardiomyopathy) a CME velocity probe positioned in the ascending aorta.

No measurement were made for at least 20 minutes after coronary arteriography. Left ventricular pressure, cardiac output, and coronary sinus flow were measured, and left ventricular and coronary sinus blood were sampled. In each of the nine patients with chest pain, and in five of the cardiomyopathy group, measurements and samples were repeated during incremental coronary sinus pacing. Left ventricular cineangiography was performed at the end of the study.

The micromanometer and thermistor signals were displayed on a Cambridge 12 channel recorder, and stored on tape. Max dP/dt was derived by an electronic differentiator or by computer, and KVmax was calculated from developed pressure¹¹ using either an electronic processor¹² or a computer. Mean left ventricular systolic pressure was derived by planimetric integration, or, when pressure and flow signals were measured simultaneously, by computer analysis¹³ Green dye curves were analysed by an IVH 3 cardiac output computer. When a velocity probe

was used, cardiac output was calculated as mean flow velocity derived from integration of the velocity signal, multiplied by aortic cross-sectional area estimated by echocardiography or aortography. Coronary sinus blood flow was measured by constant infusion thermodilution.¹⁴ Using a computer—light pen system previously described,¹² the right anterior oblique view of the left ventricular cineangiogram was analysed to yield volume, ejection fraction, and mass.

The oxygen content of heparinised blood samples was measured upon a LEX-02 CON TL. Blood was added to an aliquot of perchloric acid for subsequent estimation of concentrations of lactate and pyruvate,¹⁵ hydroxybutyrate, and acetoacetate,¹⁶ and glycerol.¹⁷ For measurement of free fatty acids¹⁸ blood was added to sequestrine tubes and centrifuged. All samples were immediately put on ice, and stored at -20°C.

Myocardial oxygen consumption was calculated as coronary sinus blood flow multiplied by the difference between arterial and coronary sinus oxygen content. The extraction of a substrate is the difference in concentration between arterial and coronary sinus blood (A-V), and extraction ratio, that difference expressed as a percentage of arterial concentration $\left(\frac{A-V}{A}\right)\%$. The oxygen extraction ratio of a substrate is defined as the amount of oxygen required to catabolise completely the amount of that substrate extracted expressed as a percentage of total oxygen extraction.

Myocardial efficiency was estimated using Bing's formula¹⁹:

$$\text{efficiency} = \frac{\text{LV minute work (kg m/min)}}{\text{Myocardial oxygen consumption (ml/min)}} \times 100\%$$

$$2.059 \times 0.806 \text{ (normal = 40\%)}$$

Values are expressed as mean \pm standard error. Student's t test and linear regression are used where appropriate, and $p < 0.05$ is considered significant.

Results

The diagnosis of congestive cardiomyopathy was confirmed in our 10 patients. Each had a dilated, poorly contracting left ventricle, normal coronary arteriograms and, with the exception of mild subvalvar mitral regurgitation, normal cardiac valves. The aetiology of myocardial damage was not identified in any patient. Two patients (cases 3 and 8) had a history suggestive of a preceding viral illness, but this was not confirmed by serology. One patient (case 1) had been a heavy drinker for many years.

Each of the nine patients investigated for chest pain (control group) had angiographically normal coronary arteries, and did not develop angina, electrocardiographic abnormalities, or produce lactate

during pacing. Basal haemodynamics and quantitative left ventricular cineangiography were normal in these patients.

BASAL HAEMODYNAMICS (Tables 1 and 2)

Basal heart rate was 99 ± 8 beats/min in the patients with cardiomyopathy and 86 ± 6 beats/min in the control subjects (NS). Cardiac index, left ventricular systolic pressure, minute work, max dP/dt, KVmax, and ejection fraction were significantly lower, and end-diastolic volume index and end-diastolic pressure significantly higher in the cardiomyopathy group than in the controls. Coronary sinus blood flow and myocardial oxygen consumption were increased in the

patients with cardiomyopathy compared with the control subjects and, as their left ventricular minute work was low, calculated efficiency was grossly reduced. None of the patients with cardiomyopathy had severe hypertrophy, though end-diastolic left ventricular free wall thickness, 0.93 ± 0.06 cm, was greater than in the control subjects, 0.69 ± 0.04 cm ($p < 0.05$). Because of this small increase in wall thickness and the large increases in cavity dimensions, left ventricular mass was significantly greater in the cardiomyopathy than in the control group. Coronary sinus blood flow and myocardial oxygen consumption normalised for ventricular mass were similar in the two groups.

Table 1 Resting haemodynamics in cardiomyopathy and control group

Case No.	Age (y)	Sex	CI (l/min per m ²)	LVSP (mmHg)	LVEDP (mmHg)	KVmax (s ⁻¹)	Max dP/dt (mmHg/s)	LVEDVI (ml/m ²)	EF
Cardiomyopathy group (n = 10)									
1	46	M	1.52	84	16	80	997	218	0.25
2	49	M	1.34	97	28	89	925	228	0.24
3	18	M	0.80	72	18	94	629	310	0.02
4	38	M	1.97	84	10	40	660	171	0.20
5	61	M	1.68	90	7	69	1145	201	0.23
6	41	M	2.02	80	15	43	920	225	0.22
7	38	F	1.80	120	17	50	900	100	0.30
8	18	M	1.24	83	28	62	609	395	0.12
9	42	M	2.18	100	6	68	1200	121	0.39
10	30	M	1.33	77	23	81	579	275	0.17
Mean	38.1		1.59*	88.7*	17*	67*	856*	224*	0.21*
SEM	4.2		0.13	4.4	2.5	6	72	31	0.04
Control group (n = 9)									
Mean	46.2		3.07	124	6.3	91.8	1527	59	0.66
SEM	5.1		0.32	8	2.0	5	58	4	0.016

* $p < 0.01$ when cardiomyopathy and control group are compared
CI, cardiac index; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; EF, ejection fraction.

Table 2 Resting haemodynamics in cardiomyopathy and control groups

Case No.	CSF (ml/min)	MVO ₂ (ml/min)	LVMW (kg m/min)	Efficiency (%)	LV mass (G)	CSF/100g (ml/min)	MVO ₂ /100g (ml/min)
Cardiomyopathy group							
1	213	19.0	2.50	7.4	291	73	6.5
2	183	15.6	2.23	8.6	216	85	7.2
3	171	35.2	0.80	1.4	315	54	11.2
4	420	48.3	2.69	3.4	390	108	12.3
5	174	32.0	2.87	5.4	222	78	14.4
6	392	52.9	2.99	5.3	340	115	15.6
7	289	35.0	3.07	5.3	181	160	19.3
8	142	21.3	0.88	1.6	190	75	11.2
9	211	26.8	4.01	9.0	248	85	10.8
10	155	21.7	0.83	2.3	365	43	5.9
Mean	235*	30.8*	2.29*	4.8*	276*	88	11.4
SEM	31	3.9	0.35	0.9	24	11	1.3
Control group							
Mean	120	11.6	6.99	39.4	121	99	9.6
SEM	15	1.6	0.63	4.0	13	10	0.8

* $p < 0.01$ when cardiomyopathy and control group are compared
CSF, coronary sinus blood flow; MVO₂, myocardial oxygen group uptake; LVMW, left ventricular minute work; CSF/100g, coronary sinus blood flow/100g myocardium; MVO₂/100g, oxygen consumption/100g myocardium.

BASAL METABOLIC RESULTS

The arterial and coronary venous concentrations, extraction, extraction ratio, and oxygen extraction ratio of the six substrates measured are listed in Table 3.

The high mean arterial lactate concentration in the cardiomyopathy group was largely the result of concentrations of 2.705 and 1.379 mmol/l in cases 3 and 8, both of whom had a very low cardiac output. Myocardial lactate production was not observed in either group. Though lactate extraction and oxygen extraction ratio were significantly greater in the cardiomyopathy than in the control group, these differences were caused in part by greater arterial lactate concentrations. Extraction ratio did not differ significantly between the two groups.

No differences were shown between the two groups in concentrations or extraction of pyruvate, hydroxybutyrate, or acetoacetate.

Free fatty acid extraction was positive in each of the patients with cardiomyopathy, whereas two of the control subjects had negative values. Extraction and extraction ratio were significantly greater in the cardiomyopathy than in the control group and these differences were still significant when the two controls with negative values were excluded from analysis.

Glycerol extraction was positive in each of the six patients with cardiomyopathy, but glycerol release was observed in six of the nine control subjects; consequently glycerol extraction and extraction ratio were significantly greater in the cardiomyopathy group.

The total of the oxygen extraction ratios of the substrates measured was $130\% \pm 18$ in the cardiomyopathy group and $86\% \pm 19$ in the control group (NS).

Effects of pacing

The results at the highest pacing rate are listed in Table 4. Pacing was without effect upon end-diastolic pressure or indices of contractility in the cardiomyopathy group, whereas in the control group end-diastolic pressure decreased and max dP/dt increased significantly. Coronary flow increased in each of the control subjects, but rose substantially in only one patient with cardiomyopathy; in two it changed little, and in two it decreased. Cardiac output decreased on pacing in both the patients who sustained large reductions in coronary flow.

Myocardial lactate production was not seen in either group during pacing, even in the two patients who sustained reductions in coronary flow.

Discussion

Although all nine patients in the control group had a history of chest pain, their normal haemodynamics and coronary arteriograms, and the failure of pacing to provoke pain or myocardial lactate production allow them to be regarded as normal control subjects.

Each of the patients in the cardiomyopathy group had reached an advanced stage of their disease. Though it is likely that within the group there were

Table 3 Basal metabolic results

	A (mM/l)	CS (mM/l)	A-V (mM/l)	A-V/A (%)	O ₂ ER (%)
Lactate					
COCM (n = 10)	0.966±0.216	0.648±0.160	0.347±0.069	35.7±3.9	19.9±3.4
Controls (n = 9)	0.562±0.066	0.407±0.044	0.134±0.032	27.5±3.6	11.1±2.2
	NS	NS	p<0.05	NS	p<0.05
Pyruvate					
COCM (n = 8)	0.057±0.013	0.036±0.008	0.0209±0.006	32.2±7.8	1.2±0.2
Controls (n = 9)	0.044±0.010	0.036±0.009	0.0179±0.010	20.0±9.1	0.6±0.2
	NS	NS	NS	NS	NS
Hydroxybutyrate					
COCM (n = 7)	0.156±0.038	0.091±0.021	0.065±0.019	42.3±6.1	5.6±1.0
Controls (n = 9)	0.188±0.053	0.121±0.035	0.066±0.019	33.6±5.5	6.9±2.1
	NS	NS	NS	NS	NS
Acetoacetate					
COCM (n = 7)	0.105±0.025	0.053±0.028	0.052±0.017	45.1±8.7	3.8±1.6
Controls (n = 9)	0.089±0.021	0.046±0.026	0.043±0.014	42.6±3.9	3.5±0.8
	NS	NS	NS	NS	NS
Free fatty acids					
COCM (n = 9)	0.753±0.114	0.539±0.080	0.225±0.037	30.2±2.5	102±18
Controls (n = 9)	0.958±0.149	0.894±0.167	0.063±0.054	7.2±7.1	61.8±18*
	NS	NS	p<0.05	p<0.01	NS
Glycerol					
COCM (n = 6)	0.076±0.014	0.056±0.014	0.020±0.004	29.2±5.8	—
Controls (n = 9)	0.064±0.001	0.074±0.007	-0.010±0.007	-12.6±8.6	—
	NS	NS	p<0.01	p<0.01	—

Values expressed as mean ± SEM. A, arterial concentration; CS, coronary sinus concentration; NS, not significant; A-V, extraction; A-V/A, extraction ratio; O₂ER, oxygen extraction ratio.

*Excluding negative values.

Table 4 Effects of pacing

Case No.	HR		LVSP		LVEDP		CO		Max dP/dt		KV max		CSF		MVO ₂		LER	
	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P	C	P
<i>Congestive cardiomyopathy</i>																		
4	91	143	84	79	10	16	3.5	2.3	660	640	40	46	420	284	48.3	31.2	34.5	24.8
6	113	170	80	80	15	22	3.9	2.0	920	920	43	60	392	247	52.9	34.0	38.7	30.0
7	90	160	120	110	17	30	3.7	3.8	900	1300	50	56	289	320	35.0	36.9	19.0	19.0
9	90	130	100	90	6	7	4.9	4.7	1200	1170	68	64	211	217	26.8	26.0	46.7	44.2
10	76	120	77	71	23	7	2.8	3.2	579	821	81	82	155	250	21.7	32.5	40.5	38.5
Mean	92	145	92	86	14	16	3.8	3.2	852	970	56	62	293	264	36.9	32.1	35.9	31.3
SEM	5.9	9.2	8	7	3	4	0.5	0.5	109	53	8	6	51	18	6	2	4.7	4.5
			NS		NS		NS		NS		NS		NS		NS		NS	
<i>Controls (n = 9)</i>																		
Mean	85	154	124	108	6	3	5.8	5.3	1527	2083	92	101	121	183	11.6	20.9	27.5	22.7
SEM	8	9	8	5	2	2	0.6	0.8	58	82	5	8	15	26	1.6	3.4	3.6	4.3
			p<0.05		p<0.05		NS		p<0.01		NS		p<0.01		p<0.01		NS	

HR, heart rate; LVSP, peak left ventricular systolic pressure (mmHg); LVEDP, left ventricular end-diastolic pressure (mmHg); CSF, coronary sinus blood flow (ml/min); MVO₂, myocardial oxygen consumption (ml/min); LER, lactate extraction ratio; C, control state; P, pacing; NS, not significant.

different causes of myocardial damage, the 10 patients were haemodynamically and metabolically so similar it is legitimate to treat them as a homogeneous group.

The efficiency of the heart can be estimated by relating external work to myocardial oxygen consumption.¹⁹ The mean value of 39% in the control group is in close agreement with previous estimates of the efficiency of the normal heart.¹⁹ Each of the patients with cardiomyopathy had low efficiency, and their mean value of 4% emphasises the severity of the disturbance of myocardial energetics. The oxygen consumption of the ventricle is determined largely by muscle tension,²⁰ dependent upon both pressure and volume, while external work is determined by the extent of muscle shortening against this tension (load). Dilatation therefore increases both myocardial oxygen consumption and the load opposing shortening. When muscle function is poor, shortening against load is reduced, so efficiency will be low, and will decrease further as energy consumption and load increase with further dilatation. That the failing dilated heart operates against excessive load is suggested by the large improvement in efficiency during infusion of sodium nitroprusside.²¹ Dilatation and excessive load are logical consequences of poor contractile function, and efficiency may be low when oxidative metabolism and the oxygen cost of tension development are normal.

The normal ventricle hypertrophies without dilating in response to chronic pressure overload, and the increased wall thickness maintains wall stress within normal limits.²² When a ventricle of a given mass dilates, the increase in cavity dimensions and decreased wall thickness will increase stress, which may stimulate hypertrophy. Though none of our patients had gross hypertrophy, their end-diastolic wall thickness was greater than in the control subjects

and their greater myocardial oxygen consumption was related largely to increased mass.

The normal heart derives its energy supply from the oxidation of free fatty acids, lactate, and glucose, with smaller contributions from the oxidation of pyruvate and ketone bodies.²³ The pattern of substrate extraction in both groups of patients was broadly similar to results reported for the normal heart.²³⁻²⁵

Myocardial lactate extraction was high in each of the patients with cardiomyopathy, and myocardial lactate production was not observed in either group. Lactate extraction and oxygen extraction ratio were significantly greater in the cardiomyopathy group than in controls. These differences may have been the result in part of the high arterial lactate concentrations observed in several patients in the cardiomyopathy group. In addition, the high arterial free fatty acid concentrations in several control subjects would be expected to inhibit myocardial lactate extraction.²⁶ The high lactate extraction in the cardiomyopathy group is consistent with the increased concentration of cytosol lactate dehydrogenase found in ventricular biopsy specimens taken from patients with this condition,⁵ though comparable lactate extraction ratios are found in patients with hypertrophic obstructive cardiomyopathy²⁷ where levels of the enzyme are normal.⁵ Moderate increases in lactate dehydrogenase have been reported in patients with poor left ventricular function secondary to chronic valvular disease.⁵ The low cardiac output of severe heart failure tends to increase arterial lactate concentration, so that increased cytosol lactate dehydrogenase levels may be a nonspecific adaptation allowing the myocardium to metabolise the available lactate.

There have been occasional reports of lactate production by the myopathic heart,^{6,7} and it has been suggested that anaerobic carbohydrate metabolism is an

important energy source in this condition.⁵ As myocardial lactate production was not observed in our patients it is unlikely that anaerobic metabolism contributed significantly to energy requirements, or that ischaemia was responsible for poor contractile function.

The study of myocardial free fatty acid metabolism is complicated by the activation of lipoprotein lipase by heparin.²⁸ We believe that adequate anticoagulation is mandatory for left heart catheterisation, and all patients in this study received heparin. In a previous study we showed that intravenous heparin administered one hour before catheterisation effectively attenuates the rise in arterial free fatty acids after a subsequent dose of heparin, and that within 30 minutes of this second dose, given at the time of arterial catheterisation, arterial concentration returns to control levels.⁸ This regimen of two doses was used in this study.

Experiments with labelled palmitate have shown that in the normal heart there is myocardial lipolysis with release of free fatty acids into coronary venous blood.²⁹ Free fatty acids extracted by the heart may be esterified rather than oxidised immediately,³⁰ and free fatty acids derived from lipolysis may be oxidised.³⁰ Thus, measured extraction may not reflect true uptake, and true uptake, if it were known, does not measure the rate of oxidation. In addition, when the arteriovenous concentration difference is narrow, small errors in measuring concentrations will have a large effect upon estimated extraction. For these reasons the finding of significantly greater free fatty acid extraction and extraction ratio in the cardiomyopathy compared with the control group should be viewed with caution.

Despite these difficulties it is of great interest that release of neither free fatty acids nor glycerol was observed in the patients with cardiomyopathy, whereas free fatty acid release was found in two, and glycerol release in six of the nine control subjects. Release of free fatty acids and glycerol are also common in patients with coronary artery disease^{8, 31} and hypertrophic obstructive cardiomyopathy.²⁷ It cannot be concluded from this study that free fatty acid metabolism is abnormal in congestive cardiomyopathy, but this problem merits further investigation with labelled free fatty acids.

Because patients with congestive cardiomyopathy improve clinically during long-term administration of beta-blocking drugs^{32, 33} and relapse when they are withdrawn,³⁴ catecholamine excess or sympathetic overactivity have been suggested as pathogenic mechanisms.^{33, 34} Acutely catecholamines increase myocardial lipolysis³⁵ and the arterial concentration and myocardial oxidation of free fatty acids,³⁶ and inhibit pyruvate dehydrogenase.³⁷ The relatively low

arterial free fatty acid concentrations, the absence of glycerol release, and the consistently high lactate extraction ratios in our patients do not suggest catecholamine excess. It is unlikely that the beneficial effect of beta-blocking drugs is the result either of changes in myocardial substrate extraction or relief of ischaemia.

In the control group the haemodynamic changes during pacing were normal,^{38, 39} whereas in the five patients with cardiomyopathy who were paced, end-diastolic pressure tended to rise and indices of contractility did not increase significantly. Coronary sinus blood flow increased substantially with heart rate in each control subject, but in only one patient with cardiomyopathy. Failure to increase flow with heart rate implies that the coronary vasculature is near maximal dilatation at rest. Under these circumstances coronary flow is critically dependent upon cardiac output and the length of diastole; in both of the patients who sustained reductions of coronary flow cardiac output decreased on pacing. Failure to augment coronary flow as heart rate increases in patients with severe aortic stenosis⁴⁰ or hypertrophic obstructive cardiomyopathy²⁷ is associated with myocardial lactate production. Lactate extraction remained high in each of our five patients. Thus, the myopathic heart does not resort to anaerobic metabolism even during the stress of pacing.

This study shows that the overall efficiency of the heart is severely reduced in congestive cardiomyopathy. Though there were small differences in substrate extraction between the two groups, no gross abnormality of oxidative metabolism was found in patients with congestive cardiomyopathy, suggesting that low efficiency lies in poor mechanical function rather than in deficient energy supply.

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