

Circulatory response to vasodilator therapy in congestive cardiomyopathy¹

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Vasodilator therapy has been shown to have beneficial effects in heart failure. In order to evaluate the haemodynamic actions of vasodilator administration in primary congestive cardiomyopathy, sodium nitroprusside was infused intravenously at a rate of 15 to 100 µg/min to 12 patients. Mean arterial pressure fell 15 per cent from 86±3.0 to 72±2.4 mmHg (11.40±0.4 to 9.6±0.3 kPa), and there was a small but significant decrease in mean heart rate from 96±4.8 to 90±4.4 beats/min. These changes were accompanied by a significant decrease in mean pulmonary artery pressure from 40±2.2 to 26±2.8 mmHg (5.3±0.3 kPa to 3.5±0.4 kPa), mean pulmonary capillary wedge pressure from 25±2.2 to 16±2.1 mmHg (3.3±0.3 to 2.1±0.3 kPa), and left ventricular end-diastolic pressure from 27±1.8 to 17±1.5 mmHg (3.6±0.3 to 2.3±0.2 kPa). Cardiac index increased by an average of 48 per cent from 2.1 to 3.1 l/min per m², and left ventricular stroke work index increased from 18.4±1.6 to 21.3±1.9 g m/m². These results show that pronounced left ventricular dysfunction in patients with congestive cardiomyopathy is improved during vasodilator therapy.

The clinical course in congestive cardiomyopathy is frequently marked by repeated episodes of cardiac failure. Progressive left ventricular dilatation is accompanied by increased left ventricular wall stress, decreased myocardial efficiency, and further depression of myocardial performance. The prognosis of these patients is poor, with almost 50 per cent dying within 12 months of the onset of pulmonary congestion, and two-thirds dying within 2 years (Hamby *et al.*, 1970).

Prolonged periods of bed rest have been advocated with modest results (McDonald, Burch, and Walsh, 1971). Diuretics and inotropic agents have been the traditional methods of treatment in an attempt to decrease left ventricular filling pressure and increase cardiac output. Such therapy may initially produce symptomatic relief; however, further deterioration is inevitable, and a downhill course ensues. Reliance on the digitalis glycosides in the setting of cardiomyopathy is associated with a high incidence of toxicity.

Reflex arteriolar vasoconstriction in heart failure produces an increased systemic vascular resistance

and impedance to left ventricular ejection, further depressing myocardial function. Recently, vasodilator therapy has been shown to improve left ventricular function in patients with congestive heart failure of diverse aetiologies (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a). In order to assess the potentially beneficial haemodynamic effects of a vasodilator agent in congestive cardiomyopathy, 12 patients were studied before and during nitroprusside infusion.

Subjects and methods

Twelve patients with congestive cardiomyopathy were investigated at the time of diagnostic cardiac catheterization. Informed consent was obtained after the nature of the study and risks were explained in detail to the patients. The subjects comprised 11 men and one woman, ranging in age from 21 to 65 years, with a mean age of 43 years. Clinically, all patients had symptoms of New York Heart Association Class III or IV severity. All had ventricular (S₃) gallop sounds and cardiomegaly. There was no history of hypertension, valvular disease, or ischaemic heart disease. Normal coronary arteries and diffuse left ventricular hypokinesis were shown angiographically in all patients, using the

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transfemoral retrograde arterial approach. All patients were taking digitalis and diuretics at the time of the study.

At cardiac catheterization, right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge phasic and mean pressures were recorded with a 7F Cournand catheter inserted via an ante-cubital vein and connected to a Stratham P23Db transducer. Arterial and left ventricular pressures were determined by percutaneous transfemoral catheterization with a 6.7F end-hole catheter connected without tubing to a micron MP-15 transducer. The frequency response of the catheter-preamplifier system was flat to 14 Hz. Zero pressure reference level was taken at mid-chest.

Cardiac output was determined by the Fick technique, using the arteriovenous O₂ difference and a 5-minute collection of expired air. Pulmonary vascular resistance and systemic vascular resistance were computed, using standard formulae. Left ventricular stroke work index was calculated using the mean left ventricular systolic pressure.

After control measurements, nitroprusside was infused intravenously, initially at a rate of 15 µg/min. The infusion rate was increased every 2 minutes by 15 µg/min until the mean arterial pressure had dropped by a minimum of 10 mmHg (1.3 kPa). Nitroprusside infusion rates of 15 to 100 µg/min were needed. Haemodynamic measurements were

repeated after 10 minutes of continuous nitroprusside infusion, maintaining the desired arterial pressure. Statistical analysis was carried out using Student's t-test for paired data.

Results

The Table summarizes the haemodynamic data in the 12 patients receiving nitroprusside. All were in sinus rhythm except one who was in atrial fibrillation. Nitroprusside produced an average fall in mean arterial pressure of 16 per cent from 86±3.0 to 72±2.4 mmHg (11.4±0.4 to 9.6±0.3 kPa). There was a small but statistically significant fall in heart rate from an average of 96±4.8 to 90±4.4 beats/min. Two patients had a modest increase in heart rate; there was no haemodynamic measure that separated them from the rest of the group. Right atrial mean pressure fell 36 per cent. Mean pulmonary artery pressure fell from 40±2 to 26±2.8 mmHg (5.3±0.3 to 3.5±0.4 kPa) (range 6 to 28 mmHg (0.8 to 3.7 kPa)), mean pulmonary capillary wedge pressure fell from 25±2.2 to 16±2.1 mmHg (3.3±0.3 to 2.1±0.3 kPa) (range 3 to 26 mmHg (0.4 to 3.5 kPa)), and left ventricular end-diastolic pressure fell from 27±1.8 to 17±1.5 mmHg (3.6±0.3 to 2.3±0.2 kPa) (range 6 to 22 mmHg (0.8 to 2.9 kPa)). These changes were all statistically significant and of similar magnitude (P < 0.001,

TABLE *Clinical and haemodynamic data in 12 patients receiving nitroprusside*

Case No., sex	R	HR (beats/min)		\overline{RA} (mmHg)		\overline{PA} (mmHg)		\overline{PCW} (mmHg)		MAP (mmHg)		LVEDP (mmHg)		CI (l/min per m ²)		LVS WI (g/m ²)		PVR (RU)		SVR (RU)	
		C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP	C	NP
1/M	NSR	88	68	5	5	42	27	33	23	79	68	32	26	2.6	3.2	22.4	29.2	2.0	0.7	16.1	10.8
2/M	NSR	71	84	23	14	53	46	36	33	93	80	32	23	2.1	3.9	16.3	18.4	6.3	3.4	34.1	17.1
3/M	NSR	120	110	23	15	47	37	28	18	104	75	26	16	2.4	3.7	26.5	28.8	3.9	0.8	16.8	7.9
4/M	NSR	90	82	4	0	49	21	37	11	76	68	42	20	1.6	2.2	11.2	15.4	4.5	2.8	28.0	19.1
5/M	NSR	108	96	9	6	38	17	26	12	104	85	28	19	2.7	4.7	28.4	30.8	2.3	0.7	15.4	10.0
6/M	NSR	80	75	8	4	28	18	16	13	76	66	20	14	2.1	2.7	19.8	20.3	2.9	1.0	16.5	12.2
7/M	NSR	95	95	9	6	28	20	16	12	88	74	20	12	1.5	2.0	16.8	17.4	4.8	2.2	27.2	18.4
8/F	NSR	84	87	11	7	42	22	26	14	86	80	26	12	2.1	4.6	20.4	30.6	4.2	1.0	20.3	8.9
9/M	AF	108	96	10	8	40	28	18	16	70	60	23	16	2.0	2.6	16.2	17.8	2.8	1.1	19.6	9.9
10/M	NSR	125	122	11	10	36	30	27	22	86	77	26	20	2.2	2.5	16.6	17.1	2.6	2.1	21.5	17.6
11/M	NSR	83	75	4	1	36	12	24	6	86	60	22	7	2.0	2.1	13.2	13.6	3.4	1.6	25.0	16.2
12/M	NSR	98	92	11	5	39	32	20	10	88	80	23	14	1.8	2.6	12.6	16.1	6.5	5.0	26.5	18.3
Mean		96	90	11	7	40	26	25	16	86	72	27	17	2.1	3.1	18.4	21.3	3.9	1.9	22.3	13.9
±SEM		4.8	4.4	1.8	1.3	2.2	2.8	2.2	2.1	3.0	2.4	1.8	1.5	0.2	0.3	1.6	1.9	0.4	0.4	1.7	1.2
Mean%Δ		-6%		-36%		-35%		-38%		-16%		37%		+48%		+16%		-51%		-38%	
P<		0.05		0.001		0.001		0.001		0.001		0.001		0.001		0.01		0.001		0.001	

R=rhythm; HR=heart rate; \overline{RA} =right atrial mean pressure; \overline{PA} =pulmonary arterial mean pressure; \overline{PCW} =pulmonary capillary wedge mean pressure; MAP=mean arterial pressure; LVEDP=left ventricular end-diastolic pressure; CI=cardiac index; LVS WI=left ventricular stroke work index; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance; RU=resistance units; C=control; NP=nitroprusside; M=male; F=female; NSR=normal sinus rhythm; AF=atrial fibrillation; SEM=standard error of the mean; mean %Δ=mean percent change.

Fig. 1). The degree of these changes did not correlate directly with the magnitude of mean arterial pressure or systemic vascular resistance decrease during nitroprusside infusion.

There was a 48 per cent mean increase in cardiac index from 2.1 ± 0.2 to 3.1 ± 0.3 l/min per m^2 (range 0.3 to 2.5 l/min per m^2). The most pronounced increases occurred in those patients with the highest left ventricular end-diastolic pressure and greatest decrease in systemic vascular resistance (Fig. 2). Systemic vascular resistance fell an average of 38 per cent, and pulmonary vascular resistance was decreased in all patients by an average of 51 per cent.

Left ventricular stroke work index rose modestly but significantly from 18.4 ± 1.6 to 21.3 ± 1.9 g m/m^2 ($P < 0.01$). The increase in left ventricular stroke work index associated with a decrease in left ventricular end-diastolic pressure suggests improved ventricular function. The most pronounced increases in stroke work index occurred in 4 to 6 patients whose initial left ventricular end-diastolic pressure was greater than 25 mmHg (3.3 kPa). Fig. 3 shows this relation by means of a standard ventricular function curve analysis.

Discussion

Patients with advanced cardiomyopathy suffer from refractory left ventricular failure. Standard therapeutic manoeuvres are aimed at increasing myocardial contractility by means of inotropic agents, and reducing left ventricular filling pressure by sodium restriction and diuretics. As the severity of pump dysfunction progresses, however, the response to such measures decreases, and intractable left ventricular failure results. In addition, intravascular volume reduction may further lower cardiac output and produce electrolyte abnormalities which may predispose to serious ventricular arrhythmias in such patients.

Recently, the importance of systemic vascular resistance and impedance to ejection have been emphasized as major determinants of left ventricular function (Cohn, 1973; Ross and Braunwald, 1964). As myocardial function decreases, the failing heart dilates, increasing end-diastolic fibre length to maintain stroke volume near normal levels (Braunwald, Ross, and Sonnenblick, 1967). Increases in ventricular filling pressure accompany the augmented

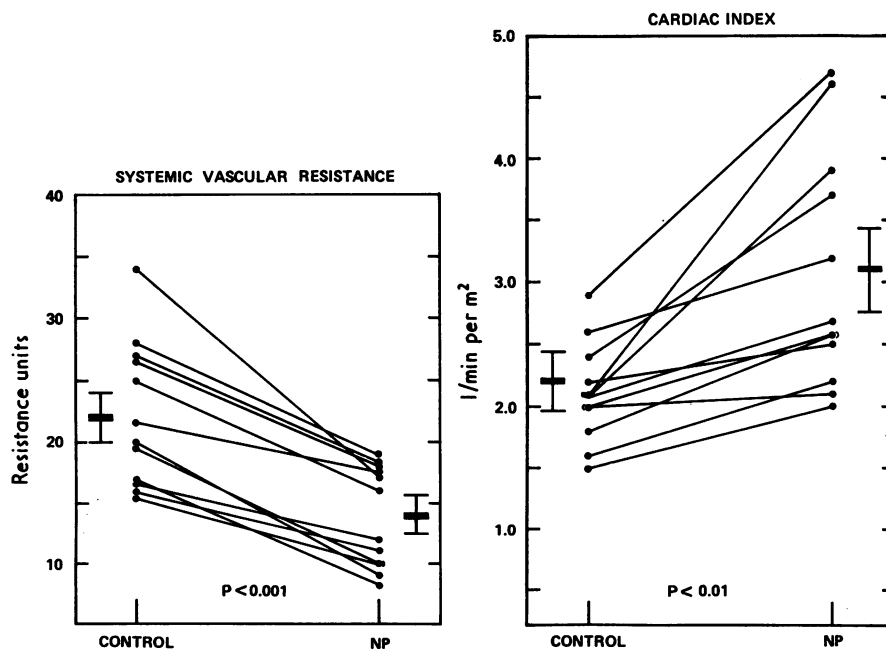


FIG. 1 Left—change in systemic vascular resistance after nitroprusside infusion. Right, change in cardiac index after nitroprusside infusion. Heavy horizontal bars indicate mean values; lighter bars indicate standard error of mean. NP=nitroprusside.

end-diastolic volume, producing symptoms of congestion. As cardiac output falls, reflex increases in circulating catecholamines produce arteriolar vasoconstriction to maintain mean arterial pressure (Chidsey, Harrison, and Braunwald, 1962; Kramer, Mason, and Braunwald, 1963). The rise in systemic vascular resistance produces an increased impedance to left ventricular ejection and, as a result, systolic ventricular wall tension or afterload is increased (Cohn, 1973). Increased afterload reduces the extent of myocardial fibre shortening, decreases the ejection fraction, and further limits pump performance (Ross and Braunwald, 1964).

Vasodilator therapy has recently been applied to patients with heart failure of various aetiologies, including acute myocardial infarction, cardiomyopathy, and mitral regurgitation (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a; Majid, Sharma, and Taylor, 1971; Walinsky *et al.*, 1974; Goodman *et al.*, 1974; Chatterjee *et al.*, 1973b). Nitroprusside was used in the present study to produce ventricular unloading in a group of patients with severe left ventricular failure. Nitroprusside infusion in our patients with chronic con-

gestive cardiomyopathy produced haemodynamic improvement consistent with previous studies (Franciosa *et al.*, 1972; Guiha *et al.*, 1974; Chatterjee *et al.*, 1973a; Miller *et al.*, 1975; Schlant, Tsagaris, and Robertson, 1962; Cohn *et al.*, 1972). Cardiac index and left ventricular stroke work index were significantly augmented while left ventricular filling pressure and right-sided cardiac pressures declined. The increase in forward output tended to parallel the fall in systemic vascular resistance (Table, Fig. 2). Thus, the reduction in impedance to left ventricular ejection produced by systolic unloading resulted in increased myocardial fibre shortening and increased stroke volume. Because heart rate, on the average, fell slightly, the increase in cardiac output primarily reflected increases in left ventricular stroke volume. In a group of patients with cardiomyopathy and intractable heart failure, Guiha *et al.* (1974) showed haemodynamic improvement of a similar magnitude. It is of note that the majority of our patients had a high left ventricular end-diastolic pressure, which was significantly reduced by nitroprusside, but which remained abnormal above 12 mmHg (1.6 kPa). Miller *et al.*

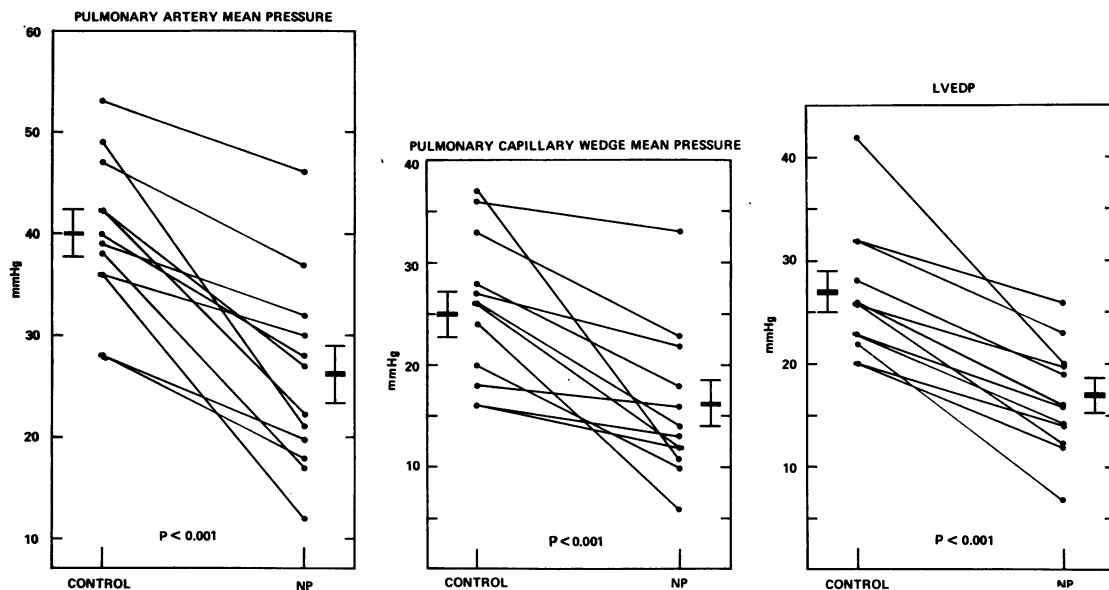


FIG. 2 Left—change in pulmonary arterial mean pressure after nitroprusside infusion. Centre—change in pulmonary capillary wedge mean pressure after nitroprusside infusion. Right—change in left ventricular end-diastolic pressure (LVEDP) after nitroprusside infusion. NP—nitroprusside. Heavy horizontal bars indicate mean values; lighter bars indicate standard error of mean.

(1975) noted that the usual beneficial response of cardiac index and heart rate to nitroprusside was not seen if left ventricular end-diastolic pressure fell below 10 mmHg (1.3 kPa). Fig. 3 supports this conclusion, in that those patients whose left ventricular end-diastolic pressure decreased to normal showed little improvement in pump performance, while those who retained some rise in left ventricular end-diastolic pressure had the greatest increase in stroke work index.

The mechanism of haemodynamic improvement during nitroprusside infusion is complex. It is clearly an arteriolar vasodilator, thus reducing systemic vascular resistance and ventricular afterload, enhancing myocardial fibre shortening, and increasing ejection fraction. In addition, nitroprusside decreases preload by dilating the peripheral venous bed (Miller *et al.*, 1975; Cohn *et al.*, 1974). Venodilatation may contribute to the lowering of systemic venous and left ventricular filling pressure. In our patients, reduction in outflow impedance appears to be primarily responsible for their improved ventricular performance.

Decreases in left ventricular end-diastolic and end-systolic volumes during nitroprusside infusion have been documented by echocardiography and angiography (Guiha *et al.*, 1974; Goodman *et al.*,

1974; Chatterjee *et al.*, 1973b; Miller *et al.*, 1975; Franciosa *et al.*, 1974). The reduction in chamber size decreases left ventricular wall tension. This, coupled with no increase in heart rate or contractile state, reduces myocardial oxygen requirements. Thus, stroke volume is increased and filling pressures are decreased in association with improved myocardial efficiency. Reduction in left ventricular volumes would be expected to decrease or abolish mitral regurgitation due to papillary muscle dysfunction, which is frequently encountered in these patients. Significant decreases in regurgitant volume and regurgitant fraction have been noted during vasodilator therapy in patients with mitral regurgitation of both valvular and subvalvular origin (Goodman *et al.*, 1974; Chatterjee *et al.*, 1973b).

The improvement in pump performance with afterload reduction documented by the present study has potentially important clinical implications. The development of long-acting oral vasodilators may offer an alternative to chronic digitalis and diuretic therapy, with their attendant complications. Recently, haemodynamic improvement with oral isosorbide dinitrate has been described in patients with congestive heart failure (Franciosa *et al.*, 1974; Cohn *et al.*, 1974). It remains to be determined whether chronic afterload reduction by oral therapy will maintain left ventricular performance, prevent progressive ventricular dilatation, and improve the prognosis of patients with congestive cardiomyopathy.

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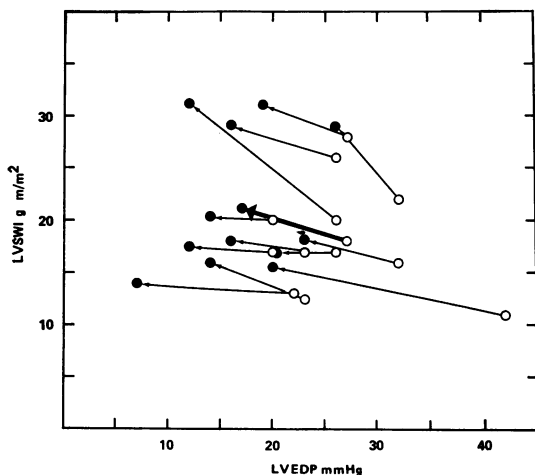


FIG. 3 Effect of nitroprusside on left ventricular stroke work index and end-diastolic pressure. Individual patients are indicated by a line connecting an open circle (control) to a closed circle (nitroprusside). Arrows indicate direction of change. Heavy line indicates mean value. LVSWI=left ventricular stroke work index. LVEDP=left ventricular end-diastolic pressure.

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