Study of left ventricular pressure-volume relations during nitroprusside infusion in human subjects without coronary artery disease¹

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SUMMARY Studies were made on 21 patients, 8 without any symptoms of left ventricular failure, group 1, and 13 with clinical symptoms of heart failure, group 2. Cardiac output, mean aortic and left ventricular pressures (using catheter tip micromanometer), and ventricular volume (obtained from left ventricular cineangiograms) were measured before and during nitroprusside infusion. The heart rate did not change in either of the groups. Only in group 2 did cardiac index and stroke volume increase significantly. Mean aortic pressure and total systemic vascular resistance decreased significantly in both the groups. Left ventricular end-diastolic pressure decreased significantly in both the groups, but this decrease was greater in group 2 (9 mmHg compared with 3 mmHg for group 1). The decrease in the left ventricular end-diastolic volume was similar in both the groups. The decrease in left ventricular end-systolic pressure was greater in group 1, but the decrease in the left ventricular end-systolic volume was greater in group 2.

These facts are explained by the differences in the active and passive left ventricular pressure-volume relations in the two groups.

Many reports (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973; Miller *et al.*, 1975; Rossen *et al.*, 1976) have shown that vasodilator therapy is effective in acute and chronic left ventricular failure. Though it leads consistently to a decrease in aortic pressure, systemic vascular resistance, and left ventricular filling pressure, the changes in cardiac output have been less uniform.

The purpose of this study was to analyse the left ventricular pressure-volume diagram before and during nitroprusside infusion and to elucidate the effects of nitroprusside on cardiac output.

Subjects and methods

After obtaining informed consent, the haemodynamic and the angiographic changes before and during nitroprusside infusion were studied in 21 patients. These were 16 men and 5 women (the age range was from 23 to 63 years). All the patients were in regular sinus rhythm. None had valvular heart

disease, septal defects, or left bundle-branch block, nor were there any clinical or electrocardiographic signs of coronary artery disease.

The patients were grouped in two categories. Group 1 comprised 8 patients who had never had symptoms of heart failure. Four had a primary hyperkinetic heart syndrome (Guazzi *et al.*, 1975). Group 2 consisted of 13 patients all of whom were in cardiac failure. Some were on diuretic therapy, but no patient was taking digitalis. All had idiopathic cardiomyopathy.

The haemodynamic data recorded before and during nitroprusside therapy were as follows. (1) Cardiac output (CO = l/min) measured by the indocyanine green dilution technique: the dye was injected into the right atrium and sampled in the main pulmonary artery through a 7 F Swan-Ganz catheter. Cardiac index (CI) and stroke volume (SV) were calculated as follows:

$$CI = \frac{CO}{BSA} \text{ (l/min per m}^2\text{), where BSA is body}$$

$$\text{surface area. } SV = \frac{CO}{HR} \text{ (ml) where HR is heart rate.}$$

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Table Haemodynamic data before (C) and during (N) nitroprusside infusion

	HR/ min		CI (l/min per m ²)		SV dye (ml)		SVA (ml)		MAP (mmHg)		TSVR dyne s ⁻¹ cm ⁻⁵		LVEDP (mmHg)	
	C	N	C	N	C	N	C	N	C	N	C	N	C	N
Group 1														
1	100	92	4.8	4.5	68	68	69	71	160	120	1882	1523	8	4
2	80	80	3.7	4.1	76	82	77	84	100	84	1311	1018	8	6
3	65	70	2.8	3.1	69	65	62	62	86	65	1528	1040	8	3
4	70	65	3.3	3.5	85	86	91	82	88	60	1315	858	6	4
5	75	95	3.8	4.3	100	90	105	72	93	78	992	734	6	3
6	110	120	6.0	6.0	72	67	60	56	90	80	900	790	6	4
7	70	80	4.0	3.5	93	71	73	63	100	70	1240	982	4	1
8	60	70	4.2	3.7	140	104	155	84	80	70	766	767	10	4
Mean	78	84	4.1	4.1	88	79	86	72	100	78	1241	964	7	4
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	17	17	0.9	0.9	24	14	31	11	25	18	360	255	2	1.4
P value	NS	NS	NS	NS	NS	NS	NS	NS	P < 0.01	P < 0.01	P < 0.01	P < 0.001	P < 0.001	P < 0.001
Group 2														
9	115	110	2.2	3.1	34	50	22	47	90	84	1800	1221	30	22
10	90	90	1.7	2.0	31	37	50	50	80	68	2245	1600	10	6
11	70	68	2.6	2.6	65	67	54	53	80	64	1406	1120	20	6
12	90	90	1.9	1.7	36	36	50	40	108	76	2468	1842	18	8
13	84	82	2.2	2.5	48	57	40	40	65	50	1238	851	30	12
14	110	100	2.0	4.2	34	77	42	75	64	54	1365	561	32	20
15	61	70	2.8	2.9	67	60	52	53	70	58	1400	1325	4	2
16	90	85	2.8	2.5	66	63	73	62	84	60	1120	980	10	3
17	70	75	1.7	2.8	51	68	45	85	86	64	1911	994	10	4
18	92	100	1.6	1.6	39	39	40	47	76	70	1688	1435	16	8
19	90	95	2.2	2.4	34	36	28	40	88	74	2270	1741	10	4
20	110	105	1.3	2.5	21	43	27	77	68	55	3820	2985	26	12
21	100	100	2.6	2.9	49	56	43	59	100	88	1632	1530	8	2
Mean	90	90	2.1	2.6	44	53	43	56	81	67	1874	1399	17	8
±	±	±	±	±	±	±	±	±	±	±	±	±	±	±
SE	16	13	0.5	0.7	15	13	13	15	13	11	719	601	10	7
P value	NS	NS	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.05	P < 0.001	P < 0.01	P < 0.01	P < 0.001	P < 0.001	P < 0.001

HR, heart rate; CI, cardiac index; SV dye, stroke volume derived from dye dilution technique; SVA, angiographic stroke volume; MAP, mean pressure; TSVR, total systemic vascular resistance; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEDSV, left ventricular end-systolic volume; EF, ejection fraction; LVESP, left ventricular end-systolic pressure; SE, standard error; NS, not significant; NP, nitroprusside.

(2) Left ventricular and ascending aortic pressures (mmHg) were recorded using a catheter tip micro-manometer (Millar 5 F). (3) The left ventricular cineangiograms were performed in the frontal plane (50 frames/s). Left ventricular volumes were calculated using the area length method of Dodge *et al.* (1966) and a grid calibration technique. The first 3 to 5 beats after injection of contrast were used for volume calculations. The post-ectopic beats were excluded.

Aortic pressure was recorded at a paper speed of 500 mm/s during the angiogram, using a micro-manometer placed in the ascending aorta. A single unit manually controlled marker permitted simultaneous synchronised measurements of angiographic films and pressure tracings from the beginning of the injection phase. It was possible to obtain the following indices before and during vasodilator infusion. (1) The systolic portion of the left ventricular pressure volume relation. The left ventricular systolic pressure was accepted as

identical to the aortic systolic pressure. (2) The variations in the instantaneous pressure-volume relation with time. Intervals were measured from the peak of the R wave of the electrocardiogram.

The end-diastolic point of the ventricular pressure-volume diagram was established from the angiographic end-diastolic volume and from the end-diastolic ventricular pressure (LVEDP) obtained immediately before angiography. In this pressure-volume diagram, the end-diastolic volume is the largest volume and the end-systolic volume (ESV) is the smallest volume. The end-systolic pressure (ESP) is the pressure related to end-systolic volume and not to the diastolic notch.

We then calculated (a) total systemic vascular resistance thus:
$$\text{TSVR} = \frac{\text{MAP} \times 80}{\text{CO}} (\text{dyne s}^{-1} \text{ cm}^{-5}),$$

where MAP is mean aortic pressure mmHg, and CO is cardiac output l/min, and (b) the left ventricular ejection fraction as:

LVEDV (ml)	LVESV (ml)		EF (%)		LVESP (mmHg)		LVESP LVESV (mmHg/ml)		Maximum value of $\frac{LVESP}{LVESV}$		Rate of NP administration ($\mu\text{g/min}$)	
	N	C	N	C	N	C	N	C	N			
130	117	61	46	53	60	185	140	3.0	3.0		15	
142	126	65	42	54	66	132	90	2.0	2.1		25	
108	95	46	33	57	65	95	75	2.1	2.3		40	
111	90	20	12	82	86	106	62	5.3	5.2		40	
138	95	33	23	76	75	108	70	3.3	3.0		30	
74	68	14	12	82	80	108	90	7.7	7.5		60	
110	91	37	28	66	70	116	80	3.1	2.9		20	
205	120	50	36	70	70	100	78	2.0	2.2		35	
127	100	41	29	67	72	119	86	3.6	3.5			
$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$			
38	19	18	13	12	10	29	24	1.9	1.9			
P < 0.05		P < 0.01		NS		P < 0.001		NS				
265	260	243	212	10	16	85	70	0.3	0.3	0.4	0.4	60
260	237	210	187	19	22	80	60	0.4	0.3	0.4	0.4	35
231	209	177	156	23	25	90	80	0.5	0.5			40
207	170	157	130	20	21	110	86	0.7	0.7			40
162	145	122	105	24	27	74	58	0.6	0.6			20
20	300	268	224	13	25	64	48	0.2	0.2	0.3	0.3	30
150	130	98	77	34	40	82	64	0.8	0.8			50
210	172	137	110	35	36	94	72	0.7	0.7			20
400	300	355	215	11	28	90	50	0.2	0.2	0.3	0.3	50
305	280	266	233	12	18	90	70	0.3	0.3	0.4	0.4	60
210	200	182	160	13	20	104	84	0.6	0.5	0.7	0.6	30
330	300	302	223	10	25	64	42	0.2	0.2			25
130	125	82	66	36	47	104	90	1.3	1.4			40
244	218	200	161	20	27	87	67	0.5	0.5			
$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$			
48	66	83	59	9	9	15	15	0.3	0.3			
P < 0.01		P < 0.01		P < 0.01		P < 0.01		NS				

$EF\% = \frac{SV}{LVEDV} \times 100$, where SV is angiographic stroke volume (ml) and LVEDV is left ventricular end-diastolic volume (ml).

Nitroprusside was infused by a flow controlled pump, 20 minutes after the first left ventricular angiogram. The initial flow rate was 10 $\mu\text{g}/\text{min}$, and this was increased every 3 to 5 minutes to obtain a stable reduction of the mean aortic pressure. The reduction in the mean aortic pressure was less than 30 mmHg except in 2 patients in whom the initial mean aortic pressure was above 100 mmHg. The simultaneous decrease of the left ventricular end-diastolic pressure was less than 10 mmHg except in 4 patients in group 2 in whom the initial left ventricular end-diastolic pressure was above 20 mmHg.

Once the pressures had become stable the nitroprusside infusion rate was maintained at a constant rate; this rate differed greatly in each patient (Table).

Results

(1) A good correlation was observed between the angiographically derived stroke volume and that obtained from the dye dilution method. The regression equation was: dye method = $6.9 + 0.89$ angio method ($n = 42$, $r = 0.88$).

(2) Changes in heart rate, cardiac index, stroke volume, mean aortic pressure, total systemic vascular resistance, and ejection fraction. The heart rate did not change significantly in either group (Table). Significant increases in cardiac index and stroke volume were observed in group 2 only ($P < 0.05$). Mean aortic pressure and total systemic vascular resistance decreased significantly in both the groups (MAP group 1 $P < 0.01$, and group 2 $P < 0.001$; total systemic vascular resistance $P < 0.01$ for both). The ejection fraction did not alter in group 1, but it increased significantly in group 2 ($P < 0.01$).

(3) Changes in left ventricular end-diastolic pressure and volume. The end-diastolic pressure

Fig. 1 Example of the instantaneous pressure-volume ratio plotted against time during ejection before (c) and during (n) nitroprusside infusion in 2 patients. (A) Patient with a normal left ventricular performance. (B) Patient with a cardiomyopathy. ∇ , onset and end of ejection.

was lower in group 1 compared with group 2 ($P < 0.01$). In both groups it decreased significantly ($P < 0.001$), in group 1 by 3 mmHg and in group 2 by 9 mmHg. The absolute decrease in group 2 was higher, but the relative decrease (that is percentage change from control) was identical in both groups. Left ventricular end-diastolic volume decreased significantly in both the groups (group 1 $P < 0.05$; group 2 $P < 0.01$). In terms of absolute value the decrease was the same in both groups (27 and 26 ml, respectively). The relative decrease was lower in patients in group 2 ($P < 0.05$) in whom the initial end-diastolic volume had been larger ($P < 0.001$).

(4) Changes in left ventricular end-systolic pressure and volume. Left ventricular end-systolic pressure decreased significantly in both the groups (group 1 $P < 0.001$; group 2 $P < 0.01$); the

relative decrease was identical. In terms of absolute values the decrease was greater in group 1 than in group 2 (33 and 20 mmHg, respectively, $P < 0.01$). The basal end-systolic pressure was higher in group 1 compared with group 2 ($P < 0.01$).

Left ventricular end-systolic volume decreased significantly in both the groups ($P < 0.01$ for both), and the relative decrease was identical. In terms of absolute values the decrease was greater in group 2 compared with group 1 (39 and 12 ml, respectively, $P < 0.05$); the initial left ventricular end-systolic volume was higher in group 2 ($P < 0.001$).

Instantaneous systolic pressure-volume ratios during ventricular ejection were identical before and during nitroprusside infusion. Towards the end of systole, the pressure-volume ratio was practically constant (Fig. 1). Thus, even though ejection time

Fig. 2 Example of the left ventricular pressure-volume diagrams before (c) and during (n) nitroprusside infusion in 2 patients (same patients as Fig. 1). (A) Patient with a normal left ventricular performance. (B) Patient with a cardiomyopathy. ∇ , onset and end of ejection.

decreased slightly, during nitroprusside, the $\frac{ESP}{ESV}$ ratio remained constant (3.6 and 3.5 in group 1; 0.5 and 0.5 in group 2) (Table). In patients in group 2 the $\frac{ESP}{ESV}$ ratio was significantly lower compared with group 1 patients ($P < 0.001$).

As the $\frac{ESP}{ESV}$ ratio was nearly the same before and during vasodilator infusion, a straight line was obtained which intersected near the origin and on which the pressure-volume diagrams ended (Fig. 2). For all the patients in group 1 and for 7 in group 2 the $\frac{ESP}{ESV}$ relations corresponded to the maximum value of instantaneous pressure-volume ratio. For 6 patients in group 2, the $\frac{ESP}{ESV}$ ratio was lower than the maximum systolic value.

Discussion

Nitroprusside has no direct positive inotropic effects on the myocardium (Chatterjee *et al.*, 1973). The effects of this agent in patients without coronary insufficiency are related to its peripheral effects on the arterial and venous systems and the resulting effects on the left ventricular loading conditions (Miller *et al.*, 1975; Rossen *et al.*, 1976).

The haemodynamic changes with nitroprusside in this study were similar to those reported previously. A drop in mean aortic pressure, left ventricular end-diastolic pressure, pulmonary wedge pressure, and systemic vascular resistance has been noted in normal subjects and in patients with arterial hypertension (Schlant *et al.*, 1962), acute myocardial infarction (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973), and chronic congestive heart failure (Miller *et al.*, 1975; Rossen *et al.*, 1976). A significant increase in cardiac output was found mainly in patients whose left ventricular filling pressures were high in the control state, remaining at the upper limit of normal during vasodilator therapy (Chatterjee *et al.*, 1973; Miller *et al.*, 1975; Rossen *et al.*, 1976). Conversely, if filling pressure decreased considerably a fall in cardiac output might result; this would be reversed by expansion of the circulating volume (Miller *et al.*, 1975).

As there were only minor changes in heart rate, changes in cardiac output were accompanied by changes in stroke volume. The changes in stroke volume after nitroprusside followed closely the

respective variations in end-diastolic volume and end-systolic volume.

During nitroprusside infusion there was a consistent decrease in left ventricular end-diastolic pressure and volume. In group 2, there was a similar reduction in left ventricular end-diastolic volume to that in patients in group 1 resulting in a larger decrease in end-diastolic pressure; this probably indicated that the patients in group 2, whose left ventricular end-diastolic pressure was higher, were on a steeper portion of the passive left ventricular pressure volume relation. However, our study does not allow evaluations of changes in left ventricular distensibility during nitroprusside infusion.

During nitroprusside infusion there was a consistent decrease in left ventricular end-systolic volume and pressure. In the patients in group 2, the decrease in end-systolic pressure was lower and the decrease in end-systolic volume was greater than in patients in group 1. This is explained by the fact

that $\frac{ESP}{ESV}$ ratio remained constant before and during

nitroprusside infusion, and also by the lower value of this ratio observed in patients in the second group.

For a given contractile state peak isovolumic pressure is linearly related to volume over the physiological range of ventricular volumes in the isolated dog heart, and the slope of this peak pressure-volume line becomes steeper as contractile state is enhanced. For the same contractile state and for the same range of ventricular end-diastolic volumes, the isolated left ventricle of the dog contracting auxotonically (that is with no isovolumic period, volume decreasing throughout systole) reaches a maximum value of the pressure-volume ratio at end-systole that lies on the same straight line as obtained by isovolumic contraction (Suga and Sagawa, 1974).

In human subjects it is impossible to obtain isovolumic pressure-volume data. Nevertheless in a preliminary study in human subjects we have shown that the end-systolic pressure-volume ratio was independent of loading changes and related to the inotropic state of the left ventricle (Merillon *et al.*, 1977): the greater the end-systolic pressure volume ratio, the better the inotropic state.

Obviously stroke volume will increase only if end-systolic volume decreases more than end-diastolic volume. The decrease in left ventricular end-diastolic volume was similar in both groups. However as the slope of the end-systolic pressure-volume relation is lower in group 2, a slight decrease in left ventricular end-systolic pressure

corresponds to a pronounced decrease in left ventricular end-systolic volume. Thus the stroke volume increased significantly only in patients from group 2.

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