Haemodynamic effects of sodium nitroprusside in 21 subjects with congestive heart failure¹

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SUMMARY Twenty-one patients in severe congestive heart failure refractory to conventional medical management were treated with sodium nitroprusside on 22 occasions. On 14 occasions (responders) there was significant improvement in clinical and haemodynamic indices. On 8 occasions (non-responders) hypotension developed without haemodynamic improvement and nitroprusside treatment had to be abandoned. The initial mean arterial pressure and the capillary wedge pressure tended to be higher in the responders while the cardiac index tended to be higher in the non-responders. The systemic vascular resistance was higher in the responders than in the non-responders (2560 ± 160 vs 1800 ± 180 dynes s cm^{-5} , $P < 0.001$). All of the responders had systemic vascular resistance greater than 1900 dynes s cm^{-5} , while only one of the non-responders had a systemic vascular resistance in this range. Thus, a variable response to vasodilator therapy for congestive cardiac failure is documented. The favourable response appears to be limited to patients with a high systemic vascular resistance.

Recent investigations have shown the effectiveness of vasodilator therapy in a number of clinical situations associated with severely impaired left ventricular function. Improvement has been shown in patients suffering from acute myocardial infarction with left ventricular failure (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973a), in those with severe mitral regurgitation (Chatterjee *et al.*, 1973b), and in the treatment of chronic congestive heart failure refractory to the usual forms of treatment (Majid *et al.*, 1971; Guiha *et al.*, 1974; Miller *et al.*, 1975).

The basis of this mode of treatment (Cohn, 1973a, b) is a reduction of impedance to left ventricular outflow by lowering the resistance of the arteriolar bed and increasing the compliance of the large arteries. There is, in addition, venous vasodilatation and a consequent increase in venous capacitance; a reduction in ventricular preload follows (Cohn *et al.*, 1972; Chatterjee *et al.*, 1973a; Miller *et al.*, 1975). The effects on the heart are a rise in ejection fraction as ventricular wall tension

declines, and a decrease in left ventricular size with an increase in stroke volume. The increase in cardiac output offsets the decreased systemic vascular resistance thus helping to maintain blood pressure at or near control levels. Myocardial oxygen is reduced since nitroprusside does not increase ventricular contractility or heart rate when used in the recommended manner.

Sodium nitroprusside has been used for this purpose because of its rapid action and high potency. Tachyphylaxis has not been noted with its use (Palmer and Lasseter, 1975). Certain safeguards are essential for its safe use, however, including measuring ventricular filling pressures, cardiac output, and systemic arterial pressure before and during its administration.

Despite its reported beneficial effects, the administration of sodium nitroprusside to patients in severe congestive failure in our coronary care unit (CCU) has, on occasion, been noted to result in a deterioration clinically as well as haemodynamically. Such deterioration occurs either acutely or even after a transient period of improvement. In this report we wish to document the varying haemodynamic responses in 21 patients who were treated with sodium nitroprusside on 22 occasions, in an attempt to provide guidelines for its safe use in the management of severe and often refractory congestive heart failure.

¹This work was supported in part by USPHS Grant, SCOR in Ischemic Heart Disease, and by the Chicago Heart Association.

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Subjects and methods

Twenty-one patients, aged 16 to 76 years (mean 50 years) of whom 17 were men and 4 women, were studied. All were in severe congestive heart failure (NYHA Class IV) which had proved refractory to maximal conventional treatment using digoxin, diuretics, bedrest, and sodium restriction.

Symptoms of failure had been present for 1 to 6 years necessitating many admissions to hospital for all these patients. The causes of the congestive cardiac failure were: coronary heart disease in 7 (documented by cardiac catheterisation in 6); congestive cardiomyopathy in 14 (documented by cardiac catheterisation in 8).

After informed consent had been obtained the patients were studied in the CCU. A Swan-Ganz balloon-flotation catheter and a 'teflon' arterial catheter were inserted under local anaesthesia into the brachial vein and artery, respectively (Resnekov and Lipp, 1971). The pulmonary capillary wedge pressure or the pulmonary artery diastolic pressure were used to approximate the left ventricular filling pressure (Falicov and Resnekov, 1970). Cardiac output was measured in duplicate using the dye dilution technique. Systemic vascular resistance was calculated as:

$$\frac{\text{MAP-RAP}}{\text{CO}} \times 80 \text{ dynes s cm}^{-5} \text{ and}$$

left ventricular stroke work index as:

$$\text{SVI} \times (\text{MAP-LVFP}) \times 0.0144 \text{ g m per m}^2$$

where MAP is mean arterial pressure, RAP is right atrial pressure (both in mmHg), SVI is the stroke volume in ml per m² body surface area, and CO is the cardiac output in l/min.

After control measurements had been made, sodium nitroprusside was administered using an infusion pump starting with a dose of 0.5 µg/kg per min and increasing until a fall in blood pressure occurred. Cardiac output and pressures were measured again and the dose of nitroprusside titrated to maximise cardiac output without unduly reducing mean arterial pressure. The therapeutic trial was stopped if the systemic arterial pressure fell to 65 mmHg or less or in patients in whom the cardiac output could not be increased without causing significant arterial hypotension. Otherwise treatment with nitroprusside continued for 2 to 7 days.

Treatment measurements contained in this report reflect those after 24 hours of nitroprusside infusion, unless the trial was stopped earlier, in which case the values shown represent the highest dose tolerated before the infusion was stopped. For purposes of analysis, patients were regarded as 'non-responders'

if the therapeutic trial was stopped because of hypotension. Patients were classified as 'responders' if an improvement in both clinical and haemodynamic indices was observed. When the patients left hospital, those classified as responders were prescribed regimens consisting of isosorbide dinitrate and, on occasion, hydralazine as well, in addition to continuing digoxin and diuretic therapy.

Results

Of the 21 patients studied, 13 showed a favourable clinical and haemodynamic response documented by an increased diuresis, decreased symptoms, lowering of the indirect left ventricular filling pressure associated with an enhanced stroke volume and cardiac index without tachycardia or hypotension. This was sustained for at least 24 hours. Seven patients, however, who failed to show any clinical or haemodynamic improvement were classified as non-responders. One patient (case 9) did respond favourably when studied first, but 18 months later when restudied failed to respond clinically or haemodynamically.

RESPONDERS

On 14 occasions there was a favourable response to the nitroprusside infusion, resembling that seen by several other observers (Guiha *et al.*, 1974; Miller *et al.*, 1975) (Fig. 1). Thus, nitroprusside reduced the systemic vascular resistance by 50 per cent or more (from 2560 ± 160 to 1070 ± 80 dynes s cm⁻⁵, $P < 0.001$) while stroke volume (29 ± 3 to 65 ± 6 ml, $P < 0.001$), cardiac index (1.5 ± 0.1 to 3.0 ± 0.20 l/min per m², $P < 0.001$), and stroke work index (14 ± 2 to 30 ± 3 g m per m², $P < 0.001$) approximately doubled. Mean arterial blood pressure fell (from 98 ± 4 to 79 ± 3 mmHg, $P < 0.001$), while the average heart rate declined insignificantly (from 94 ± 6 to 84 ± 5). The indirect left ventricular filling pressure also fell by almost one-half (from 36 ± 3 to 21 ± 1 mmHg, $P < 0.001$) (Table A).

These haemodynamic changes were accompanied by evidence of clinical improvement in the cardiac failure and by an enhanced diuresis.

Follow-up of the patients which was maintained for 2 to 24 months after the study revealed that 4 deaths occurred during this time, 3 of which were directly attributed to their cardiac disease.

NON-RESPONDERS

Treatment with nitroprusside was discontinued on 8 occasions because an improvement in cardiac output could not be achieved without compromising the blood pressure. On 7 occasions, there was a transient period of improved cardiac output and lowered

Fig. 1 Haemodynamic values during control (C) and nitroprusside infusion (NP) measurements in responders (R) and non-responders (NR).

Table Summary of haemodynamic data

<i>no.</i>	<i>Age (y)</i>	<i>Mean arterial pressure (mmHg)</i>	<i>Left ventricular filling pressure† (mmHg)</i>	<i>Cardiac output (l/min)</i>	<i>Cardiac index (l/min per m²)</i>	<i>Heart rate/min</i>	<i>Stroke volume (ml/stroke)</i>	<i>Systemic vascular resistance (dynes s cm⁻⁵)</i>	<i>Stroke work index (g m per m²)</i>								
		<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>	<i>C</i>	<i>NP</i>		
<i>responders</i>																	
44		110	80	45	20	2.7	7.3	1.4	3.6	118	125	23	56	2670	830	11	25
65		120	105	32	16	3.9	5.3	2.0	2.7	80	68	49	79	2460	1580	32	53
38		90	80	30	25	2.4	6.6	1.3	3.6	96	96	25	69	2800	910	11	29
50		120	90	60	25	2.4	4.5	1.3	2.4	124	88	19	51	3400	1510	9	25
56		85	80	40	20	2.5	6.3	1.4	3.4	63	68	40	93	2400	890	14	43
45		117	97	20	20	3.2	8.2	1.5	3.8	101	84	31	101	2670	940	21	51
60		93	70	30	20	3.1	4.6	2.1	3.1	90	78	29	59	2190	1130	18	31
25		85	75	33	15	2.6	7.2	1.5	4.1	92	98	28	75	2480	730	12	36
55		73	65	40	20	2.3	4.0	1.2	2.2	132	80	17	50	1980	1090	4	18
43		100	70	40	30	2.9	5.2	1.7	3.1	88	88	33	59	2060	920	16	20
16		95	70	35	23	2.1	3.5	1.2	2.0	110	97	19	36	2860	1260	10	28
40		90	80	35	30	2.8	5.0	1.6	2.8	90	84	31	60	2000	1000	10	22
60		92	65	30	20	3.3	5.9	1.7	3.0	60	60	56	98	1930	680	15	27
60		95	80	30	15	1.4	3.9	0.8	2.5	68	68	12	28	4000	1440	14	16
Mean		98	79	36	21	2.7	5.5	1.5	3.0	94	84	29	65	2560	1070	14	30
SEM		4	3	3	1	0.2	0.4	0.1	0.2	6	5	3	6	160	80	2	3
P		<0.001		<0.001		<0.001		<0.001		NS		<0.001		<0.001		<0.001	
<i>non-responders</i>																	
35		75	72	25	20	4.4	3.8	2.0	1.8	108	108	41	33	1280	1510	14	11
57		75	80	24	15	3.1	2.4	1.5	1.1	96	112	32	26	1680	1830	11	11
27		95	70	30	25	2.3	1.8	1.5	1.1	120	96	19	20	2960	2700	11	8
76		75	70	25	22	4.1	5.8	2.2	3.2	88	98	47	66	1460	870	19	29
72		80	70	25	20	3.0	3.4	1.7	1.9	72	72	42	47	1840	1930	18	19
25		95	75	30	30	4.7	3.8	2.4	1.9	90	88	50	43	1440	1360	23	17
53		75	70	25	15	3.1	2.9	1.8	1.7	88	85	35	34	1780	1930	14	19
57		77	70	22	22	2.9	2.0	1.4	1.2	80	80	36	27	1900	2800	12	8
Mean		81	72	26	21	3.5	3.2	1.8	1.7	93	92	38	37	1800	1800	15	15
SEM		3	1	1	2	0.3	0.5	0.1	0.2	5	5	3	5	180	230	2	2
P		<0.050		<0.010		NS		NS		NS		NS		NS		NS	

Each subject was studied on two separate occasions separated by an 18-month interval. * indicates significant difference between control and NP values. C, control; NP, nitroprusside.

systemic vascular resistance, but thereafter (usually within 16 hours) the mean arterial pressure fell to unacceptable levels. Six patients had a decrease in cardiac output. Two patients (cases 18 and 19) experienced a modest increase in cardiac output which was insufficient to maintain the mean arterial pressure in the face of the decreased peripheral resistance. As a result, the group as a whole demonstrated no change in cardiac output, systemic vascular resistance, stroke volume, or stroke work index, despite a drop in arterial pressure from 81 ± 3 to 72 ± 1 ($P < 0.05$) (Table B). The capillary wedge pressure also fell, from an average of 26 ± 1 to 21 ± 2 ($P < 0.01$). Several of these patients subsequently required dopamine to maintain the blood pressure despite stopping nitro-

prusside. No patients experienced any untoward symptoms during the nitroprusside infusion (and no myocardial infarctions were documented).

Six of the non-responders died between 2 weeks and 2 months after study. All the deaths were attributed to cardiac failure and its complications.

Discussion

On the basis of the data obtained from the 21 patients studied it is recommended that when treatment with nitroprusside is being considered for the management of severe cardiac failure, particular attention should be paid not only to an assessment of left ventricular filling pressure but also to the level of the systemic vascular resistance.

Comparison of the control data for the two groups showed that they could not be distinguished on the basis of age, aetiology of failure, the physical signs, or by renal function. However, the haemodynamic data showed (see Fig. 2) that mean arterial pressure tended to be higher for the responders than for the non-responders (98 ± 4 vs 81 ± 3 , $P < 0.005$) as did left ventricular filling pressure (36 ± 3 vs 26 ± 1 , $P < 0.005$). Cardiac index tended to be higher for the non-responders (1.5 ± 0.1 vs 1.8 ± 0.1 , $P < 0.005$), while stroke volume and stroke work index were not significantly different between the two groups. There was, however, an overlap between the two groups making it difficult to predict the response in any individual patient. The systemic resistance was higher in the responders than in the non-responders (2560 ± 160 vs 1800 ± 180 , $P < 0.01$) and, while all responders had a systemic vascular resistance greater than 1900 dynes $s\ cm^{-5}$, only one non-responder had one in this range. Fisher's exact test (Brownlee, 1960) revealed the difference in systemic vascular resistance to be a significant prognostic indicator ($P < 0.001$).

Reports to date have emphasised the benefits of vasodilator therapy in congestive failure. The results obtained in this study suggest that there exists a group of patients in whom vasodilator therapy is not beneficial. An adverse response to nitroprusside has been noted to be associated with normal or low ventricular filling pressures in both acute myocardial infarction (Chatterjee *et al.*, 1973a) and in chronic ischaemic heart disease (Miller *et al.*, 1975). In this study the observations that the indirect left ventricular filling pressure tended to be higher in the group that responded to treatment supports the importance of assessing left ventricular filling pressure before and during treatment with nitroprusside. In none of our patients, however, did nitroprusside reduce the raised indirect left ventricular filling pressure to the normal range.

Fig. 2 Control haemodynamic values in non-responders (NR) and responders (R). SVR, systemic vascular resistance (dynes $s\ cm^{-5}$); MAP, mean arterial pressure (mmHg); LVFP, indirect left ventricular filling pressure (mmHg); CI, cardiac index ($l/min\ m^2$).

The importance of knowing the systemic vascular resistance before using nitroprusside is shown by the fact that it was, in fact, the single most useful index for predicting the response. The raised systemic vascular resistance in those who respond favourably appears to be an inappropriate compensatory mechanism, the effect of which is to reduce cardiac output by increasing the afterload and thus opposing ventricular ejection. In contrast, however, in those who failed to respond to sodium nitroprusside, the systemic vascular resistance was closer to the normal range and attempts to reduce it were not associated with any improvement in the status of the patients. Thus, in those who do not respond to nitroprusside left ventricular dysfunction appears to be less dependent on afterload.

As shown by the haemodynamic measurements in the 21 patients congestive cardiac failure represents a heterogeneous syndrome. Ventricular filling pressure and systemic resistance vary greatly between patients and in the extent to which they compromise or support left ventricular function. Vasodilator therapy appears to be of most value in those in whom high afterload plays an important role in left ventricular dysfunction, and in whom ventricular filling pressures greatly exceed normal values.

The authors wish to express their appreciation for the invaluable assistance of the nursing and technical staff of the Coronary Care Unit.

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