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Haemodynamic effects of nifedipine in heart failure

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SUMMARY Nifedipine, a calcium antagonist with strong vasodilatating effects, has been successfully used in the treatment of angina pectoris. To investigate if it can be used as a vasodilator in patients with congestive heart failure, nifedipine 20 mg was administered sublingually to 11 patients with chronic heart failure. The clinical diagnosis was congestive cardiomyopathy in 10 and severe mitral regurgitation in one patient. All patients were studied haemodynamically and in 10 of them an angiographic study was also performed.

Nifedipine lowered mean systemic arterial pressure (from $95{\cdot}0 \pm 5{\cdot}3$ to $75{\cdot}2 \pm 3{\cdot}6$ mmHg), mean pulmonary arterial pressure (from $37{\cdot}9 \pm 3{\cdot}1$ to $28{\cdot}0 \pm 2{\cdot}4$ mmHg), mean pulmonary capillary wedge pressure (from $25{\cdot}2 \pm 2{\cdot}0$ to $16{\cdot}7 \pm 1{\cdot}7$ mmHg), left ventricular end-diastolic pressure (from $22{\cdot}6 \pm 1{\cdot}8$ to $14{\cdot}2 \pm 1{\cdot}7$ mmHg), and systemic vascular resistance (from 1967 ± 247 to 1108 ± 146 dynes s cm^{-5}). Simultaneously all indices of left ventricular performance improved: cardiac index rose from $2{\cdot}12 \pm 0{\cdot}11$ to $3{\cdot}11 \pm 0{\cdot}30$ l/m² per min, ejection fraction increased from $0{\cdot}26 \pm 0{\cdot}02$ to $0{\cdot}41 \pm 0{\cdot}05$ per cent, and stroke volume index rose from $32{\cdot}2 \pm 1{\cdot}9$ to $46{\cdot}8 \pm 3{\cdot}4$ ml/m². Left ventricular end-diastolic volume index and end-systolic volume index both diminished (from $137{\cdot}2 \pm 14{\cdot}0$ to $128{\cdot}1 \pm 14{\cdot}3$ ml/m² and from $104{\cdot}9 \pm 13{\cdot}6$ to $81{\cdot}3 \pm 14{\cdot}7$ ml/m², respectively). No significant changes in heart rate were noted, whereas a slight general improvement in left ventricular wall motion was seen.

In patients with congestive heart failure, there were no negative inotropic effects but an improvement in left ventricular performance in all patients, caused by a decrease in afterload secondary to the strong vasodilatating effect of the drug.

Further studies should document the possibility of nifedipine being used as an alternative to other afterload reducing agents in the chronic treatment of heart failure.

Systemic vasodilator drugs have been used increasingly during recent years in the treatment of heart failure.[1–3] These agents decrease the oxygen consumption and enhance the performance of the failing heart,[4] by reducing left ventricular wall tension in systole (afterload) and/or decreasing systemic venous return.

Nifedipine is a drug with a calcium antagonist action which has proved to be particularly effective in the treatment of angina pectoris.[5–7] The main actions of this drug in man are a reduction of peripheral resistance[8 9] and an increase in coronary flow especially in post-stenotic areas.[10 11]

Considering its effects on the peripheral resistance vessels and the low incidence of side effects,[12] nifedipine may be useful as a vasodilator in the treatment of chronic heart failure.

The purpose of this study is to evaluate the acute haemodynamic effects of the administration of nifedipine in patients with chronic congestive heart failure.

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Subjects and methods

Studies were made on 11 patients (age 41 to 67 years) with persistent heart failure despite appropriate treatment with digitalis, diuretics, and salt restriction (Table 1). The clinical diagnosis was congestive cardiomyopathy in 10 patients and congestive heart failure secondary to severe mitral regurgitation in one patient. Severe exertional dyspnoea was the predominant symptom and all the patients had radiographic cardiomegaly and upper lobe blood redistribution. There was no history of ischaemic heart disease. Informed consent was obtained from all patients. Diuretics were withdrawn 24 hours before the procedure. The day before the study, nifedipine, 10 mg, was given sublingually and the blood pressure was measured at

10-minute intervals during 40 minutes of observation.

CARDIAC CATHETERISATION

At the time of the study the patients were in a fasting state without premedication. Either a Cournand (7 or 8 F) or an angiographic (7 F) end-hole catheter was placed in the pulmonary artery via an antecubital vein. Left heart catheterisation was performed either by a brachial artery cutdown using a Lehman catheter (7 or 8 F) or by the Seldinger technique using a pigtail catheter (8 F). A polythene catheter (PE 205) was inserted in the descending aorta (Seldinger technique). In eight patients a right atrial catheter was placed (Cournand 6 or 7 or NIH 6 F) via the left femoral vein.

All pressure measurements were recorded on an Electronics for Medicine VR 6 recorder, with P 23 Db Statham strain gauge transducers and zero was set at the mid-chest level. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was determined by the Fick technique using a three-minute collection of expired air.

Thirty degrees right anterior oblique left ventricular cineangiograms (64 frames/s) were obtained both before and 40 minutes after nifedipine by the injection of 45 to 60 ml of Urografin 76 (meglumine diatrizoate and sodium diatrizoate) at 12 to 18 ml/s in 10 patients. In one patient (case 11) angiography was not performed because of the risk of pulmonary oedema.

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS AND CALCULATIONS

Quantitative angiographic measurements were obtained using a light-pen computer system (Mennen Greatbatch system 939 digital PDP 11 computer) which employs the area-length method of Sandler and Dodge.[13]

Segmental wall motion was quantified according to the method of Leighton *et al.*[14] Both premature and the first postpremature beats were excluded. For the patients (cases 1 and 4) in atrial fibrillation three cardiac cycles were averaged. The following calculations were made: $CI = CO/BSA$ (l/min per m^2); $SVR = 80 \times (\overline{AP} - \overline{RA})/CO$ (dynes s cm^{-5}); $PVR = 80 \times (\overline{PA} - \overline{PCW})/CO$ (dynes s cm^{-5}); TPR

Table 1 *Biographical data and baseline haemodynamic values*

Case no.	Age (y)	Sex	Diagnosis	Period	CI (l/m² per min)	HR (beats/min)	$\overline{SAP}$ (mmHg)	$\overline{RAP}$ (mmHg)	$\overline{PA}$ (mmHg)	$\overline{PCW}$ (mmHg)	LVEDP (mmHg)
1	59	M	COCM, AF	C	2·4	98	114	6	41	22	24
				B	2·4	98	114	6	41	22	24
2	45	M	COCM	C	1·9	74	96	3	14	5	9
				B	2·0	60	98	5	23	13	14
3	57	M	COCM	C	2·4	60	100	7	17	15	21
				B	2·6	63	114	7	21	20	32
4	64	M	COCM, AF	C	1·8	70	73	7	32	23	15
				B	2·1	70	76	5	28	25	14
5	63	M	COCM	C	3·1	84	115	7	40	27	19
				B	2·3	90	100	8	35	28	18
6	63	M	COCM	C	2·2	80	92	6	36	27	24
				B	2·5	80	96	7	44	30	26
7	67	M	COCM	C	1·6	70	140	15	60	28	20
				B	1·6	70	120	16	55	29	18
8	56	M	COCM	C	2·0	71	76	12	35	33	30
				B	2·0	70	75	12	37	33	30
9	66	F	CHF, MR	C	1·5	100	104	6	45	35	22
				B	1·4	95	105	9	45	37	23
10	41	M	COCM	C	2·4	80	74	12	40	25	23
				B	2·4	88	74	18	47	28	24
11	55	M	COCM	C	—	—	—	—	—	—	—
				B	2·0	76	74	8	41	28	26
Mean ± SEM (11 patients)				B	2·12 ±0·11	78·1 ±3·9	95·0 ±5·3	9·3 ±3·1	37·9 ±3·1	25·2 ±2·0	22·6 ±1·8
Mean ± SEM (10 patients)				C	2·13 ±0·15	78·7 ±4·0	98·4 ±6·7	8·1 ±1·1	36·0 ±4·1	24·0 ±2·7	20·8 ±1·7
				B	2·13 ±0·12	78·4 ±4·3	97·2 ±5·4	8·7 ±1·1	37·6 ±3·4	26·5 ±2·1	22·3 ±1·9
p value C vs B (10 patients)					NS	NS	NS	NS	NS	<0·01	NS

COCM, congestive cardiomyopathy; CHF, congestive heart failure; AF, atrial fibrillation; MR, mitral regurgitation; C, initial haemodynamic values; B, haemodynamic values immediately before nifedipine administration; CI, cardiac index; HR, heart rate; SAP, mean systemic arterial pressure; $\overline{RAP}$, mean right atrial pressure; $\overline{PA}$, mean pulmonary artery pressure; $\overline{PCW}$, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

$=80 \times \overline{PA}/CO$ (dynes s cm^{-5}), where CI = cardiac index, CO = cardiac output, BSA = body surface area, $\overline{AP}$ = mean aortic pressure, SVR = systemic vascular resistance, $\overline{RA}$ = mean right atrial pressure, 80 = factor for converting resistance units to dynes s cm^{-5}, PVR = pulmonary vascular resistance, $\overline{PA}$ = mean pulmonary artery pressure, $\overline{PCW}$ = mean pulmonary capillary wedge pressure, TPR = total pulmonary resistance.

STUDY PROCEDURE

Heart rate, systemic arterial, right atrial, pulmonary arterial, pulmonary wedge, and left ventricular pressures were recorded. Cardiac output was determined. Left ventricular angiography was performed and immediately afterwards all the pressure measurements were repeated. At five-minute intervals the left ventricular end-diastolic pressure was measured until it returned to control values and then all the control measurements were repeated. In those patients in whom the left ventricular end-diastolic pressure remained high, a maximum of 30 minutes elapsed[15] before control measurements were repeated.

Nifedipine 20 mg was then administered sublingually. All pressures were recorded after 10, 20, and 30 minutes. Cardiac output was determined 20 and 30 minutes after the drug was administered. At 40 minutes a second left ventriculogram was performed. All the measurements (except cardiac output) were recorded immediately afterwards.

All values were expressed as mean ± SEM. Student's t test on paired data was used for statistical analysis. P values < 0·05 were considered significant.

Results

The haemodynamic data before and 30 minutes after the 20 mg sublingual dose of nifedipine are shown in Table 2. All patients responded with an increase in cardiac index (mean increase +46%), which was moderate in some, but in two cases was more than 70 per cent (cases 2 and 11). The substantial increase in cardiac index was accompanied by a distinct decrease in systemic vascular

Table 2 *Haemodynamic effects of nifedipine*

Case no.	*Period*	*CI (l/m² per min)*	*HR (beats/min)*	*$\overline{SAP}$ (mmHg)*	*$\overline{RAP}$ (mmHg)*	*$\overline{PA}$ (mmHg)*	*$\overline{PCW}$ (mmHg)*	*LVEDP (mmHg)*	*SVR (dynes s cm^{-5})*	*PVR (dynes s cm^{-5})*	*TPR (dynes s cm^{-5})*
1	B	2·4	98	114	6	41	22	24	2032	357	771
	N	3·3	87	82	6	21	15	9	1021	80	282
2	B	2·0	60	98	5	23	13	14	2199	236	544
	N	5·5	80	72	3	15	5	5	604	87	131
3	B	2·6	63	114	7	21	20	32	1505	14	295
	N	3·2	80	90	7	18	8	10	951	114	206
4	B	2·1	70	76	5	28	25	14	1682	71	663
	N	2·3	60	64	5	23	21	11	1285	43	501
5	B	2·3	90	100	8	35	28	18	1562	118	594
	N	2·7	113	96	8	32	22	13	1285	146	467
6	B	2·5	80	96	7	44	30	26	1663	261	822
	N	3·5	76	81	3	28	18	12	1045	134	375
7	B	1·6	70	120	16	55	29	18	3364	841	1779
	N	2·3	60	72	11	36	23	15	1401	298	827
8	B	2·0	70	75	12	37	33	30	1371	87	805
	N	2·3	66	65	12	37	22	24	1004	284	701
9	B	1·4	95	105	9	45	37	23	3639	303	1706
	N	1·8	90	84	4	27	17	15	2318	289	1000
10	B	2·4	88	74	18	47	28	24	1018	345	854
	N	3·7	82	63	13	39	28	20	588	129	458
11	B	2·0	76	74	10	41	28	26	1600	315	994
	N	3·5	82	59	9	32	21	23	689	151	441
Mean ± SEM	B	2·12 ± 0·11	78·1 ±3·9	95·0 ±5·3	9·3 ±1·3	37·9 ±3·1	25·2 ±2·0	22·6 ±1·8	1967 ±247	268 ±67	893 ±138
	N	3·11 ± 0·30	79·6 ±4·5	75·2 ±3·6	7·3 ±1·0	28·0 ±2·4	16·7 ±1·7	14·2 ±1·7	1108 ±146	159 ±27	490 ±79
p value		< 0·01	NS	< 0·0005	< 0·025	< 0·001	< 0·00025	< 0·0025	< 0·0005	NS	< 0·001

B, haemodynamic values immediately before nifedipine administration; N, haemodynamic values 30 minutes after nifedipine administration; CI, cardiac index; HR, heart rate; $\overline{SAP}$, mean systemic arterial pressure; $\overline{RAP}$, mean right atrial pressure; $\overline{PA}$, mean pulmonary artery pressure; $\overline{PCW}$, mean pulmonary capillary pressure; LVEDP, left ventricular end-diastolic pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance.

resistance (−43%) and by a moderate decline in mean systemic arterial pressure (−21%). Left ventricular end-diastolic pressure fell in all patients (−37%). Mean pulmonary artery and mean pulmonary wedge pressures decreased significantly (−26 and −34%, respectively). Only six patients showed a change in mean right atrial pressure. The average decline was −21 per cent and was significant ($p < 0.025$). Pulmonary vascular resistance fell by an average of 40 per cent but this change was not significant. In the seven patients with high resistances (> 120 dynes s cm^{-5}), this fall was significant (Fig. 1) and was well correlated with the pretreatment values (Fig. 2).

There was no significant change in heart rate: four patients had a small increase, and seven patients a small decrease in heart rate.

Angiographic results are shown in Table 3. All patients showed an increase in stroke volume and ejection fraction (+45 and +57%, respectively) and a decrease in left ventricular end-systolic volume (−22%). Left ventricular end-diastolic volume decreased significantly (−6%), but in two patients (cases 7 and 10) showed a slight increase. Changes in segmental systolic shortening are shown in Fig. 3.

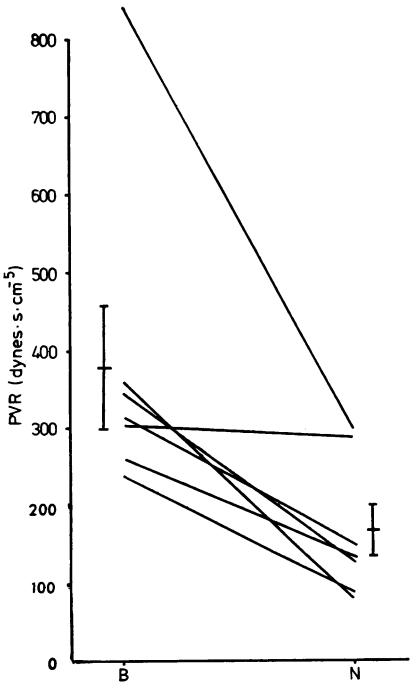

Fig. 1 *Change in pulmonary vascular resistance after nifedipine administration in the seven patients with high (> 120 dynes s cm^{-5}) resistance (mean ± SEM). Cases 1, 2, 6, 7, 9, 10, 11. B, basal; N, nifedipine.*

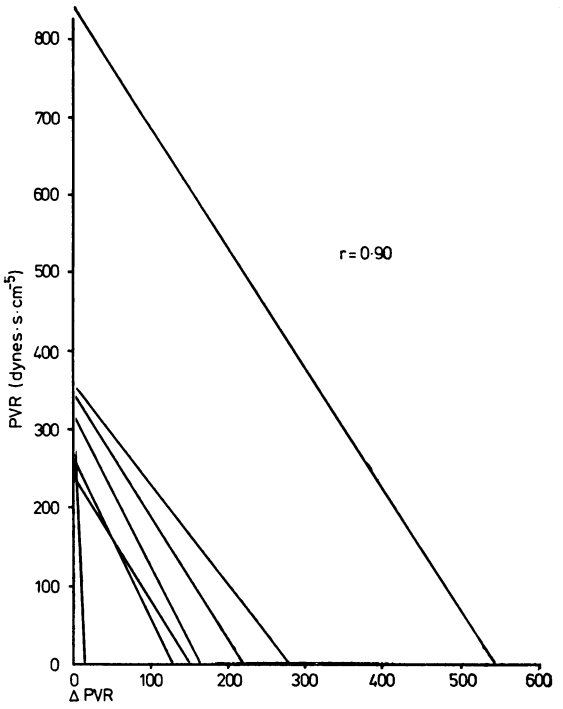

Fig. 2 *Fall in pulmonary vascular resistance (ΔPVR) compared with initial values (PVR) in seven patients of Fig. 1.*

Discussion

Congestive heart failure is characterised by a decreased cardiac output and an augmented left ventricular end-diastolic pressure. An increase in systemic vascular resistance helps to maintain systemic arterial pressure, but this leads to augmented impedance to left ventricular ejection. Systemic vasodilators may interrupt this vicious cycle by increasing left ventricular emptying and diminishing myocardial oxygen consumption,[4] and they are assuming a new role in the treatment of heart failure.[2 3] Nifedipine is a calcium antagonist drug which reduces systemic vascular resistance.[9 16] This effect (with the consequent reduction in left ventricular afterload) and the increase in coronary flow[10 11] are the main mechanisms of action of this drug in ischaemic heart disease. The rapidity and efficacy of nifedipine mediated reduction of peripheral resistance,[9] moreover, suggested that it might represent a first choice drug in hypertensive emergencies.[16] The negative inotropic action of nifedipine, initially described in the isolated heart muscle preparation,[17] was not shown in the haemodynamic studies which followed in man. The

pronounced vasodilatating effect, not accompanied by any change in contractility, may be explained by the in vitro observation that the excitation-contraction coupling of vascular smooth muscle is three to 10 times more sensitive than myocardial fibres to the action of calcium antagonist drugs.[18] The vasodilatating effect, therefore, can be achieved even at a dosage inadequate to act on myocardial contractility. In haemodynamic studies in man a slight increase in peak dP/dt has been observed in some subjects.[9 16 19] This may be a result of the baroceptor mediated response to a fall in arterial pressure. In this study nifedipine was used to reduce impedance to ventricular emptying in a group of patients suffering from chronic congestive heart failure.

In the group studied, nifedipine determined important haemodynamic changes (Table 2). There was a significant fall in mean pulmonary artery, mean aortic, and left ventricular end-diastolic pressure, a decrease in systemic vascular and total pulmonary resistance, and a significant increase in cardiac index. Angiographic derived data (Table 3) also showed an improvement in left ventricular performance, as evidenced by an increase in ejection fraction and stroke volume and a decrease in both left ventricular end-diastolic and end-systolic volumes. Segmental shortening analysis (Fig. 3) indicated a diffuse hypokinesis in all patients and showed a general but not statistically significant improvement.

Table 3 *Changes in angiographic derived values after nifedipine*

Case no.	*Period*	*LVEDVI (ml/m²)*	*LVESVI (ml/m²)*	*SVI (ml/m²)*	*EF (%)*
1	C	111·2	77·4	33·9	0·30
	N	92·4	56·5	35·9	0·39
2	C	113·5	85·1	28·4	0·25
	N	106·6	45·7	60·9	0·57
3	C	109·8	70·3	39·4	0·36
	N	93·2	27·6	65·6	0·70
4	C	167·8	146·4	21·4	0·13
	N	160·3	123·1	37·2	0·23
5	C	91·9	59·7	32·2	0·35
	N	82·6	49·8	32·8	0·40
6	C	178·8	146·1	32·8	0·18
	N	163·6	120·5	43·1	0·26
7	C	67·3	41·5	25·8	0 38
	N	70·4	27·4	43·0	0·61
8	C	171·4	132·1	39·3	0·23
	N	158·4	112·7	46·2	0·29
9	C	153·1	123·3	29·7	0·19
	N	143·6	86·8	56·8	0·40
10	C	207·0	167·5	39·5	0·19
	N	210·1	162·9	47·2	0·22
Mean ± SEM	C	137·2 ± 14·0	104·9 ± 13·6	32·2 ±1·9	0·26 ±0·02
	N	128·1 ± 14·3	81·3 ± 14·7	46·8 ±3·4	0·41 ±0·05
p value		< 0·005	< 0·00025	< 0·0025	< 0·0025

LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index; EF, ejection fraction; C, control; N, 40 minutes after nifedipine administration.

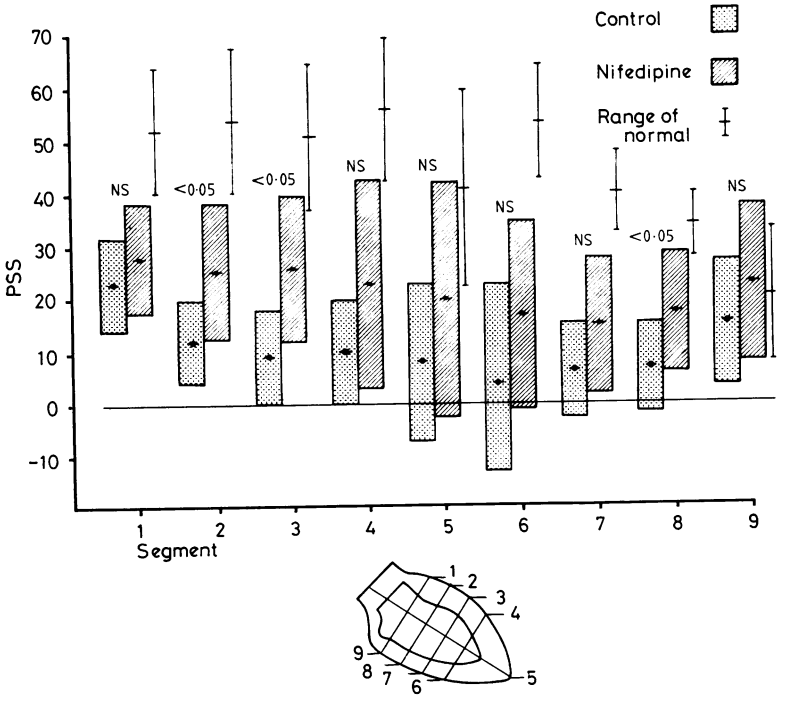

Fig. 3 Top: *Changes in percentage of systolic shortening (PSS) for nine segments considered, compared with normal values (mean ± SD).* Bottom: *Identification of nine segments on ventricular silhouette.*

Nifedipine exerts in vitro a pronounced relaxation on vascular smooth muscle,[18] and this finding was subsequently confirmed in studies undertaken in man.[9 16] It is likely, therefore, that afterload reduction, resulting from arteriolar vasodilatation, is responsible for the haemodynamic changes and the improvement in left ventricular performance observed in our patients. The fall in systemic vascular resistance was more pronounced in the patients with high initial resistance levels (Fig. 4) and this may suggest that nifedipine acts predominantly where arteriolar tone is higher. The effect of nifedipine on pulmonary vascular resistance is similar and consistent with this suggestion.

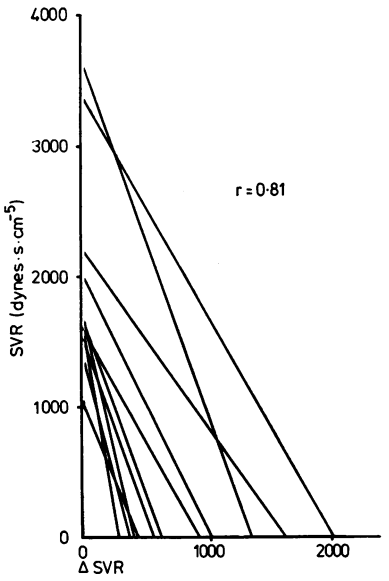

Fig. 4 *Fall in systemic vascular resistance (ΔSVR) compared with initial values (SVR) in 11 patients studied.*

A significant decrease took place only in the seven patients with high resistance (Fig. 1) and was well correlated with the initial resistance levels (Fig. 2). The decrease in right atrial pressure that occurred only in a few patients does not necessarily mean that nifedipine acts directly on preload, and it may be explained by the improvement in ventricular emptying which follows the reduction of arterial impedance. That nifedipine does not act on preload is supported by other data showing no venous pooling effect after the administration of the drug.[20]

Previous and present data indicate that nifedipine is an active afterload reducing agent. Since nifedipine, in vitro, exerts a negative inotropic effect, it is thus likely that the observed increase in ejection fraction and stroke volume is secondary to the afterload reduction and not a direct inotropic effect on the heart. Nifedipine has already been used to treat hypertensive emergencies.[16] Present data suggest that it can also be safely used to provide a rapid and distinct ventricular unloading in patients with left ventricular failure and raised systemic vascular resistance. There are still several problems, however, concerning the use of nifedipine as an alternative to vasodilator drugs currently used for the long-term treatment of heart failure.

Further studies are needed to document the duration of the acute haemodynamic effects in patients with heart failure. Previous observations in hypertensive patients showed a significant effect still persisting two hours after a 10 mg oral dose. Further studies, moreover, should determine whether the observed haemodynamic changes persist during long-term treatment and if any undesirable effects are associated with drug dosages higher than those used in the treatment of angina pectoris.

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References

[1]Majid PA, Sharma B, Taylor SH. Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 1971; **2**: 719–24.

[2]Chatterjee K, Parmley WW. Vasodilator treatment for acute and chronic heart failure. *Br Heart J* 1977; **39**: 706–20.

[3]Mason DT. Afterload reduction and cardiac performance. Physiologic basis of systemic vasodilators as a new approach in the treatment of congestive heart failure. *Am J Med* 1978; **65**: 106–25.

[4]Cohn JN. Vasodilator therapy for heart failure. The influence of impedance on left ventricular performance. *Circulation* 1973; **48**: 5–8.

[5]Hashimoto K, Kimura E, Kobayashi T. *New therapy of ischemic heart disease.* Tokyo: University of Tokyo Press, 1974.

[6]Lochner W, Braasch W, Kroneberg G. *2nd International Adalat® symposium. New therapy of ischemic heart disease.* Berlin: Springer, 1975.

[7]Jatene AD, Lichtlen PR. *3rd International Adalat® symposium. New therapy of ischemic heart disease. International congress series.* Amsterdam: Excerpta Medica, 1976: 388.

[8]Lydtin H, Lohmoller R, Schmitz H, Walter I. Haemodynamic studies on Adalat in healthy volunteers and in patients. In: Lochner W, Braasch W, Kroneberg G, eds. *2nd International Adalat® symposium. New therapy of ischemic heart disease.* Berlin: Springer, 1975: 112.

[9]van den Brand M, Remme WJ, Meester GT, Tiggelaar-de Widt I, de Ruiter R, Hugenholtz PG. Changes in left and right ventricular haemodynamics in angina pectoris patients following Adalat administration. In: Jatene AD, Lichtlen PR, eds. *3rd International Adalat® symposium. New therapy of ischemic heart disease.* Amsterdam: Excerpta Medica, 1976: 69–75.

[10]Lichtlen PR, Engel HJ, Amende I, Rafflenbenl W, Simon R. Mechanism of various antianginal drugs. Relationship between regional flow behaviour and contractility. In: Jatene AD, Lichtlen PR, eds. *3rd International Adalat® symposium. New therapy of ischemic heart disease.* Amsterdam: Excerpta Medica, 1976: 14–29.

[11]Lichtlen PR, Engel HJ, Hundeshagen H. Regional myocardial blood flow in normal and poststenotic areas after nitroglycerin, beta blockade (atenolol), coronary dilatation (dipyridamole), and calcium antagonism (nifedipine). *Herz* 1977; **2**: 81–6.

[12]Ebner F, Dünschede HB. Haemodynamic, therapeutic mechanism of action and clinical findings of Adalat use based on worldwide clinical trials. In: Jatene AD, Lichtlen PR, eds. *3rd International Adalat® symposium. New therapy of ischemic heart disease.* Amsterdam: Excerpta Medica, 1976: 283–300.

[13]Sandler H, Dodge HT. The use of single plane angiograms for the calculations of left ventricular volume in man. *Am Heart J* 1968; **75**: 325–34.

[14]Leighton RF, Wilt SM, Lewis RP. Detection of hypokinesis by a quantitative analysis of left ventricular cineangiograms. *Circulation* 1974; **50**: 121–7.

[15]Brown AK, Epstein EJ, Coulshed N, Clarke JM, Doukas NG. Haemodynamic changes after angiocardiography. *Br Heart J* 1969; **31**: 233–45.

[16]Guazzi M, Olivari MT, Polese A, Fiorentini C, Magrini F, Moruzzi P. Nifedipine, a new antihypertensive with rapid action. *Clin Pharmacol Ther* 1977; **22**: 528–32.

[17]Landmark K, Refsum H. The effect of Adalat on the mechanical and electrical activity of isolated rat cardiac muscle, with special reference to calcium antagonism of the compound. In: Lochner W, Braasch W, Kroneberg G, eds. *2nd International Adalat® symposium. New therapy of ischemic heart disease.* Berlin: Springer, 1975: 101.

[18]Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977; **17**: 149–66.

[19]Piegas LS, Paes Neto F, Konstadinis T, Mahalgães HM, de Souza JEMR, Jatene AD. Haemodynamic evaluation of a new antianginal drug: nifedipine. In: Jatene AD, Lichtlen PR, eds. *3rd International Adalat® symposium. New therapy of ischemic heart disease.* Amsterdam: Excerpta Medica, 1976: 76–92.

[20]Mostbeck A, Partsch H, Peschl L. Investigations on peripheral blood distribution. In: Jatene AD, Lichtlen PR, eds. *3rd International Adalat® symposium. New therapy of ischemic heart disease.* Amsterdam: Excerpta Medica, 1976: 91–106.

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