Acute haemodynamic effects of nifedipine in patients with ventricular septal defect

SALI BERISHA, ARTAN GODA, ADNAN KASTRATI, ARJAN FRASHERI, YLLI POPA

From the Division of Cardiology, Hospital 1, Tirana, Albania

SUMMARY The haemodynamic effects of nifedipine were studied in 14 patients (aged 8-14 years, seven male and seven female) with ventricular septal defect with and without pulmonary hypertension. All underwent left and right heart catheterisation. In each patient the pressures and heart rate were measured and blood samples were taken for oximetry before and after sublingual administration of 10 mg nifedipine.

In eight patients with ventricular septal defect without pulmonary hypertension (mean pulmonary artery pressure < 20 mm Hg) nifedipine significantly reduced the mean aortic pressure and systemic vascular resistance, and significantly increased heart rate. The other haemodynamic indices did not change significantly.

In six patients with ventricular septal defect complicated by pulmonary hypertension (mean pulmonary artery pressure > 20 mm Hg) nifedipine significantly increased systemic output, stroke volume, and heart rate, and significantly reduced systemic vascular resistance and the pulmonary to systemic flow ratio. The other haemodynamic indices did not change significantly.

Nifedipine had a beneficial effect in patients with ventricular septal defect complicated by pulmonary hypertension. It reduced the left to right shunt and increased the stroke volume. This effect was not seen in patients with ventricular septal defect uncomplicated by pulmonary hypertension.

Vasodilators are important and original agents for the treatment of congestive heart failure from various causes.¹⁻³ Their beneficial effects are more pronounced in the congestive heart failure secondary to valvar regurgitation⁴⁻⁶ and to mechanical complications of acute myocardial infarction.^{7,8} The reduction of peripheral vascular resistance has been followed by a substantial improvement of cardiac pump function, increased cardiac output, and attenuation of the clinical signs of venous and systemic congestion in these patients.^{1,5,6}

In animals with experimental ventricular septal defect vasodilators significantly reduced systemic vascular resistance, pulmonary to systemic flow ratio, and left to right shunt, and caused a considerable increase in the forward blood flow across the aorta.^{9,10} Opposite effects were seen with vasopressor drugs.¹¹ Clinical studies in patients with ventricular septal

defect and congestive heart failure confirmed these data.¹²⁻¹⁴

This study was designed to evaluate the acute haemodynamic effects of nifedipine in children with ventricular septal defect with and without pulmonary hypertension.

Patients and methods

We studied 14 children (seven male and seven female, aged 8-14 years) with isolated ventricular septal defect. Six patients were being treated for congestive heart failure—five with digitalis and diuretics and one with diuretics. In all of them treatment was stopped at least 24 hours before cardiac catheterisation. Informed consent was obtained from their parents. Right and left heart catheterisation was then performed in fasting patients after premedication with 1 mg/kg of intramuscular pethidine hydrochloride. Pressures were measured by fluid filled catheters connected to Bentley-Trantec Model 800 pressure transducers. The pressure signals and one electrocardiographic

Requests for reprints to Dr Sali Berisha, Klinika e Kardiologjise, Spitali 1, Tirana, Albania.

Accepted for publication 30 November 1987

Table 1 Clinical data and treatment in patients with ventricular septal defects without pulmonary hypertension (group A) and with pulmonary hypertension (group B)

Case	Age (years)	Sex	CTR	Liver* (cm)	Treatment	
					Digitalis	Diuretics
Group A:						
1	8	F	0.58	1	—	—
2	13	M	0.50	1	—	—
3	12	M	0.56	2	—	+
4	12	M	0.53	NE	—	—
5	8	M	0.60	1	—	—
6	14	F	0.53	NE	—	—
7	9	F	0.58	2	+	+
8	10	F	0.59	NE	—	—
Group B:						
9	11	F	0.62	1	—	—
10	8	F	0.59	3	+	+
11	12	M	0.63	3	+	+
12	14	F	0.60	1	+	+
13	10	M	0.58	2	+	+
14	8	M	0.57	1	—	—

*Centimetres below right costal margin.

CTR, cardiothoracic ratio; NE, no enlargement.

lead were recorded by a CGR 1000 apparatus at a paper speed of 50 mm/s. Blood samples from the aorta, pulmonary artery, left and right ventricle, right atrium, and superior and inferior vena cava were drawn to measure oxygen saturation and content. Oxygen consumption was measured by the flow-through method.¹⁵ Systemic and pulmonary

blood flows were derived from the Fick method. The pulmonary to systemic flow ratio (Qp/Qs) and systemic and pulmonary vascular resistance were then calculated by means of known formulae. All the haemodynamic and oximetric data were obtained before and 30 minutes after sublingual administration of 10 mg nifedipine. Each procedure was completed with left ventriculography that confirmed the presence of ventricular septal defect.

Patients with a mean control pulmonary artery pressure ≤ 20 mm Hg were assigned to group A (n = 8) and those with mean control pulmonary artery pressure > 20 mm Hg to group B (n = 6).

STATISTICAL ANALYSIS

A two tailed *t* test for paired observations was used to compare differences between means. *p* values of < 0.05 were considered to be statistically significant. All values are expressed as mean (SD).

Results

Tables 1 and 2 shows the clinical findings and the haemodynamic data for each patient respectively.

GROUP A

Nifedipine administration significantly reduced the mean aortic pressure from 85.1 (12.7) to 80.6 (13.1) mm Hg (*p* = 0.01) and the systemic vascular

Table 2 Haemodynamic data before (C) and after nifedipine (N) administration in patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension (group B)

Case	HR (beats/min)		Ao (mm Hg)		PA (mm Hg)		RA (mm Hg)		LVEDP (mm Hg)		Qp (l/min)		Qs (l/min)		SVR (dyn.s.cm ⁻⁵)		PVR (dyn.s.cm ⁻⁵)		Qp/Qs	
	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N	C	N
Group A:																				
1	110	120	94	88	20	20	4.0	4.0	9	9	7.7	12.3	4.7	4.8	1515	1388	146	71	1.62	2.54
2	70	95	75	65	12	13	3.0	1.0	2	0	7.8	8.8	5.5	7.8	1049	657	108	118	1.42	1.13
3	100	135	85	78	15	14	1.9	1.3	2	4	6.7	5.6	3.4	3.8	1814	1609	156	118	1.81	1.47
4	89	120	88	88	15	18	1.0	0.0	5	5	6.4	8.9	4.7	5.7	1481	1237	125	117	1.36	1.56
5	112	128	84	84	20	25	2.5	4.5	7	8	12.0	10.8	7.9	8.1	825	597	86	95	1.52	1.31
6	120	150	72	66	13	15	2.5	3.5	5	7	6.4	7.3	4.2	3.5	1312	1419	94	104	1.52	2.08
7	84	93	73	72	12	13	3.5	3.5	6	6	9.3	12.8	6.2	7.8	941	703	52	41	1.50	1.64
8	110	130	110	104	17	14	2.5	1.3	3	3	11.2	11.2	7.6	7.0	1139	1173	100	79	1.48	1.59
Mean	99.4	121.4	85.1	80.6	15.5	16.5	2.6	2.4	4.9	5.3	8.4	9.7	5.5	6.1	1259.5	1097.0	108.4	92.9	1.53	1.67
(SD)	(17.0)	(19.4)	(12.7)	(13.1)	(3.3)	(4.2)	(0.9)	(1.7)	(2.5)	(2.9)	(2.2)	(2.5)	(1.6)	(1.9)	(332.4)	(391.8)	(33.6)	(27.6)	(0.14)	(0.45)
p	0.003		0.011		NS		NS		NS		NS		NS		0.026		NS		NS	
Group B:																				
9	100	100	100	90	70	55	6.0	4.0	8	4	10.2	9.4	3.3	4.0	2253	1713	492	434	3.05	2.31
10	86	98	90	80	76	65	7.5	7.0	12	10	7.6	9.1	3.3	4.0	2000	1460	674	583	2.30	2.27
11	96	102	82	84	70	75	2.5	5.5	7	10	3.9	3.5	4.5	5.0	1480	1264	1280	1496	0.87	0.70
12	108	120	80	70	52	34	3.8	3.2	12	12	15.2	15.6	4.3	5.4	1416	984	128	112	3.53	2.89
13	72	77	96	88	24	29	3.0	3.5	10	6	7.4	8.4	5.4	6.6	1390	1021	152	219	1.38	1.27
14	75	85	88	94	30	30	3.0	3.5	7	7	8.0	9.9	2.7	4.4	2538	1633	229	186	3.00	2.23
Mean	89.5	97.0	89.3	84.3	53.7	48.0	4.3	4.5	9.3	8.2	8.7	9.3	3.9	4.9	1846.2	1345.8	492.5	505.0	2.25	1.63
(SD)	(14.3)	(14.9)	(7.8)	(8.5)	(22.3)	(19.7)	(2.0)	(1.5)	(2.3)	(3.0)	(3.8)	(3.9)	(1.0)	(1.0)	(488.9)	(307.7)	(440.7)	(516.0)	(1.04)	(0.80)
p	0.016		NS		NS		NS		NS		NS		0.003		0.003		NS		0.032	

HR, heart rate; Ao, mean aortic pressure; PA, mean pulmonary arterial pressure; RA, mean right atrial pressure; LVEDP, left ventricular end diastolic pressure; Qp, pulmonary blood flow; Qs, systemic blood flow; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Qp/Qs, pulmonary to systemic flow ratio.

Fig 1 Effect of nifedipine on systemic blood flow in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; Q_s , systemic blood flow.

resistance from 1259.5 (332.4) to 1097.8 (391.8) dyn.s.cm^{-5} ($p = 0.026$); it significantly increased the heart rate (from 99.4 (17.0) to 121.4 (19.4) beats/min) ($p = 0.003$). There were non-significant changes in pulmonary vascular resistance (from 108.4 (33.6) to 92.9 (27.6) dyn.s.cm^{-5}), cardiac output (from 5.5 (1.6) to 6.1 (1.9) l/min), stroke volume (from 57.4 (12.6) to 65.7 (29.6) ml), pulmonary blood flow (8.4 (2.2) to 9.7 (2.5) l/min), pulmonary to systemic flow ratio (from 1.53 (0.14) to 1.67 (0.45)), mean pulmonary artery pressure (from 15.5 (3.3) to 16.5 (4.2) mm Hg), left ventricular end diastolic pressure (from 4.9 (2.5) to 5.3 (2.9) mm Hg), and mean right atrial pressure (from 2.6 (0.9) to 2.4 (1.7) mm Hg).

GROUP B

In this group there were significant increases in cardiac output (fig 1) (from 3.9 (1.0) to 4.9 (1.0)

Fig 2 Effect of nifedipine on systemic vascular resistance in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; SVR, systemic vascular resistance.

Fig 3 Effect of nifedipine on pulmonary to systemic flow ratio in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; QP/Q_s , pulmonary to systemic flow ratio.

l/min, $p = 0.005$), stroke volume (from 44.8 (15.5) to 52.0 (17.1) ml, $p = 0.02$), and heart rate (from 89.5 (14.3) to 97.0 (14.9) beats/min, $p = 0.016$) after nifedipine administration. Systemic vascular resistance fell significantly (fig 2) (from 1846.2 (488.9) to 1345.8 (307.7) dyn.s.cm^{-5} , $p = 0.003$), as did the pulmonary to systemic flow ratio (fig 3) (from 2.36 (1.04) to 1.95 (0.80), $p = 0.032$). There were non-significant changes in mean aortic pressure (from 89.3 (7.8) to 84.3 (8.5) mm Hg), mean pulmonary artery pressure (from 53.7 (22.3) to 48.0 (19.7) mm Hg), pulmonary vascular resistance (fig 4) (from 492.5 (440.7) to 505.0 (516.0) dyn.s.cm^{-5}), left ventricular end diastolic pressure (from 9.3 (2.3) to 8.2 (3.0) mm Hg), pulmonary blood flow (fig 5) (from 8.7 (3.8) to 9.3 (3.9) l/min), and mean right atrial

Fig 4 Effect of nifedipine on pulmonary vascular resistance in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; PVR, pulmonary vascular resistance.

Fig 5 Effect of nifedipine on pulmonary blood flow in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; QP, pulmonary blood flow.

pressure (from 4.3 (2.0) to 4.5 (1.5) mm Hg). The only patient with a bidirectional shunt showed an increase in the right to left shunt (from 47 to 51%) after nifedipine.

Control values of systemic vascular resistance were higher in group B than in group A (fig 6) (1846.2 (488.9) *v* 1259.5 (332.4) dyn.s.cm⁻⁵, *p* = 0.02). Group B also showed a greater decrease in systemic vascular resistance after nifedipine (fig 7) 500.3 (232.2) *v* 161.6 (161.9) dyn.s.cm⁻⁵, *p* = 0.007). The magnitude of the change in systemic vascular resistance caused by nifedipine correlated well with its control value in all patients (fig 8) (*r* = 0.68, *p* = 0.003).

Fig 6 Comparison of control values of systemic vascular resistance between patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension. SVR, systemic vascular resistance.

Fig 7 Comparison of changes in systemic vascular resistance caused by nifedipine between patients with ventricular septal defect without pulmonary hypertension (group A) and with pulmonary hypertension (group B) (changes are expressed as differences between control and post-treatment values). SVR, systemic vascular resistance.

Discussion

This study showed that the acute haemodynamic response to nifedipine in patients with ventricular septal defect complicated by pulmonary hypertension differs from that in patients without this complication.

After nifedipine the systemic flow and stroke volume increased and the pulmonary to systemic flow ratio decreased significantly in patients with ventricular septal defect and raised mean pulmonary

Fig 8 Relation between the control values of systemic vascular resistance and the magnitude of change after nifedipine in all the patients (changes are expressed as differences between baseline values and values after treatment). SVR, systemic vascular resistance.

arterial pressure (group B); whereas these variables did not change significantly in patients with ventricular septal defect and normal mean pulmonary artery pressure (group A). Shunting at the ventricular level, with its resultant chronic volume overload, is the basic haemodynamic anomaly in ventricular septal defect. In patients with ventricular septal defect, the haemodynamic conditions in which left ventricular emptying occurs are very similar to those created by mitral regurgitation. The defect in the ventricular septum and the regurgitant mitral valve constitute a low impedance path for a portion of cardiac output.

Lowering left ventricular afterload by means of vasodilators (hydralazine) was associated with a 50% increase in the forward stroke volume and a 33% decrease in the regurgitant volume in a group of patients with mitral regurgitation.⁴ These changes were dependent upon the extent to which systemic vascular resistance was reduced, as shown by another study of nitrates.⁵ Experimental studies of ventricular septal defect showed that the amount of interventricular shunting was largely determined by the left ventricular afterload.⁹⁻¹¹ The left to right shunt was increased by the infusion of pressor amines¹¹ and reduced (by 33%) after α blockade with phentolamine and phenoxybenzamine.⁹ A considerable decrease was seen after hydralazine administration and even more with prazosin.¹⁰ In clinical studies too hydralazine significantly increased the systemic blood flow in patients with a large ventricular septal defect.¹²⁻¹⁴ Vasodilators do not have a constant action on systemic vascular resistance, pulmonary flow, and pulmonary to systemic flow ratio. Several studies of vasodilator treatment reported increased systemic flow and reduced pulmonary to systemic flow ratio.¹²⁻¹⁴ In other studies these measurements did not change or changed in only some cases.^{14,16} Indeed there are reports of a significant increase in pulmonary to systemic flow ratio and systemic vascular resistance in response to these agents.^{17,18} The results of these studies and ours demonstrate that patients with ventricular septal defect can react in various ways to vasodilator drugs. Their response seems to be determined by several factors: the type and size of the defect itself,^{9,10} the values of systemic and pulmonary vascular resistance, and in particular the left ventricular preload and performance.¹⁶⁻¹⁸

In patients with congestive heart failure of various causes vasodilators improve left ventricular ejection and augment cardiac output by reducing the raised systemic vascular resistance; this mechanism, however, may not be active in all cases of ventricular septal defect: it is probably absent in those patients with ventricular septal defect who have normal systemic vascular resistance and left ventricular

performance¹² as did most of group A patients in our study (these indices were normal in five of our eight patients). In fact, in group A patients nifedipine substantially reduced systemic vascular resistance (which was normal in this group as a whole) and mean arterial pressure, increased heart rate without appreciably altering systemic and pulmonary blood flow, pulmonary to systemic flow ratio, mean pulmonary arterial pressure, or pulmonary vascular resistance. Furthermore, systemic vascular resistance was reduced in this group, but this reduction was probably insufficient to induce a significant change in the pulmonary to systemic flow ratio. On the other hand, this group had normal control values for pulmonary vascular resistance. This mechanism is important, however, in patients with ventricular septal defect and abnormally raised systemic vascular resistance.^{14,16} Evidence from experimental and clinical studies showed that in patients with small and restrictive ventricular septal defects and normal pulmonary vascular resistance, the amount of the left to right shunt was related to the size of the defect and to the level of systemic vascular resistance; the shunt was augmented by raising the systemic vascular resistance with pressor amines¹¹ and lowered by decreasing the raised systemic vascular resistance with vasodilators.^{10,12} This effect was seen in patient 9, who had a ventricular septal defect of moderate size with raised systemic vascular resistance and normal pulmonary vascular resistance. Nifedipine induced a consistent increase in systemic blood flow and a reduction in the pulmonary to systemic flow ratio, owing to a fall in systemic vascular resistance. By contrast, in patients with a large and non-restrictive ventricular septal defect, the amount of the interventricular shunt was primarily dependent on the pulmonary to systemic resistance ratio¹⁹⁻²¹; the effects of vasodilators in these patients are therefore determined by the responsiveness of the pulmonary and systemic circulation to these agents. A greater pulmonary to systemic vascular resistance ratio will be associated with a smaller left to right shunt, assuming all other factors remain constant.¹⁷

Vasodilator drugs dilate the systemic and pulmonary vascular bed in patients with congestive heart failure of various aetiologies.¹⁻³ Their effect in the pulmonary circulation is not, however, constant. Nifedipine and other vasodilators do not always succeed in lowering pulmonary vascular resistance²²; indeed in other studies an increase has been seen.²³⁻²⁵ This was present in patients 3 and 5 in group B. In patients with large ventricular septal defects, raised pulmonary vascular resistance (owing to functional changes), and normal or slightly increased systemic vascular resistance, vasodilator drugs may affect the pulmonary vascular bed more than the systemic one,

thereby increasing the left to right shunt. Similar evidence was derived from studies with nitroprusside^{17,18} and hydralazine.¹⁶ The same effect was seen in our patient 7 in whom nifedipine reduced systemic vascular resistance but also reduced pulmonary vascular resistance by 50%, thus increasing the left to right shunt. Preload reduction is important in the increase of pulmonary to systemic flow ratio caused by nitroprusside.¹⁷ Patients with ventricular septal defect, abnormally raised systemic vascular resistance, and reduced systemic blood flow will respond differently to vasodilators, particularly if the pulmonary vascular bed does not react to these agents because of fixed obstructive structural changes. It is the magnitude of reduction of the systemic vascular resistance that determines the decrease in pulmonary to systemic flow ratio and the increase of systemic blood flow in response to vasodilators in this group of patients. Nifedipine considerably reduced systemic vascular resistance, increased systemic blood flow and stroke volume, and reduced the pulmonary to systemic flow ratio in patients with pulmonary hypertension (group B). In this group of patients pulmonary blood flow did not change and, unlike patients without pulmonary hypertension (group A), neither did mean aortic pressure. The increases in systemic blood flow and venous return seem to have prevented the decrease of pulmonary blood flow and mean aortic pressure even in the presence of a reduced left to right shunt and reduced systemic vascular resistance.

The increase in systemic blood flow and venous return seem to have prevented both the diminished left to right shunt from reducing pulmonary blood flow and reduced systemic vascular resistance from lowering mean aortic pressure. The appreciable reduction in systemic vascular resistance was responsible for the significant increase of systemic blood flow and decrease of pulmonary to systemic flow ratio in our patients because in both groups neither pulmonary vascular resistance nor the left and right ventricular preload showed any significant change in response to nifedipine.

Our study shows that the magnitude of reduction of the systemic vascular resistance by nifedipine in our patients was a function of the pretreatment value because (a) the decrease in systemic vascular resistance was significantly greater in group B (in which systemic vascular resistance was higher) than in group A, and (b) the size of the change in systemic vascular resistance after nifedipine correlated well with its control value. A similar correlation was shown in other studies of vasodilators in patients with congenital or acquired heart disease. In a group of patients with valvar regurgitation the reduction in systemic vascular resistance by nitrates was more

pronounced in those with higher control values.⁵ In another study in patients with large ventricular septal defect and pulmonary hypertension hydralazine caused a larger decrease in systemic vascular resistance (29%) in patients with systemic vascular resistance of > 20 units.m² than in patients with systemic vascular resistance < 20 units.m² (only 6%).¹⁴

We conclude that in patients with ventricular septal defect and pulmonary hypertension, nifedipine significantly reduced Qp/Qs and substantially increased systemic blood flow; this had a beneficial effect on the fundamental haemodynamic disturbance in patients with a left to right shunt. Nifedipine exerts its haemodynamic effect by lowering systemic vascular resistance.

References

- 1 Majid PA, Sharma B, Taylor SH. Phentolamine for vasodilator treatment of severe heart failure. *Lancet* 1971;ii:719-23.
- 2 Chatterjee K, Parmley WW. The role of vasodilator therapy in heart failure. *Prog Cardiovasc Dis* 1977;19:301-25.
- 3 Franciosa JA. Effectiveness of long-term vasodilator administration in the treatment of chronic left ventricular failure. *Prog Cardiovasc Dis* 1982;24:319-32.
- 4 Greenberg BJ, Massie BM, Brundage BH, Botvinik EH, Parmley WW, Chatterjee K. Beneficial effects of hydralazine in severe mitral regurgitation. *Circulation* 1978;28:273-9.
- 5 Goldberg S, Mann T, Grossman W. Nitrate therapy of heart failure in valvular heart disease. *Am J Med* 1978;65:161-4.
- 6 Goodman DY, Rossen RM, Holloway EL, Alderman EL, Harrison DC. Effects of nitroprusside on left ventricular dynamics in mitral regurgitation. *Circulation* 1974;50:1025-32.
- 7 Techlenberg PL, Fitzgerald J, Allaire BI, Alderman EL, Harrison DC. Afterload reduction in the management of postinfarction ventricular septal defect. *Am J Cardiol* 1976;38:956-8.
- 8 Radford EY, Johanson AR. Ventricular septal rupture: review of clinical and physiologic features and analysis of survival. *Circulation* 1981;64:545-53.
- 9 Synhorst DP, Lauer RM, Doty DD, Brody MY. Hemodynamic effects of vasodilator agents in dogs with experimental ventricular septal defect. *Circulation* 1976;54:472-7.
- 10 Boucek MM, Chang R, Synhorst DP. Effects of prazosin and hydralazine on the hemodynamics of chronically instrumented lambs with ventricular septal defect [Abstract]. *Circulation* 1980;62(suppl III):111-115.
- 11 Tanenbaum H, Pfaff W. Effect of pressor amines on experimental intracardiac shunts and valvular regurgitation. *Dis Chest* 1963;44:485-91.
- 12 Beekman RH, Rocchini AP, Rosenthal A. Hemodynamic effects of hydralazine in infants with a large ventricular septal defect. *Circulation* 1982;65:523-8.

- 13 Cloez JL, Isaaz K, Marchal C, Morizot D, Pernot C. Effets hemodynamiques d'un vasodilateur alpha-bloquant dans l'insuffisance cardiaque par shunt gauche-droite de l'enfant. *Arch Mal Coeur* 1986;79:671-82.
- 14 Nakazawa M, Takao A, Chan Y, Shimizu T, Kanaya K, Kazuo M. Significance of systemic vascular resistance in determining the hemodynamic effects of hydralazine on large ventricular septal defects. *Circulation* 1983;68:420-4.
- 15 Lister G, Hoffman JIE, Rudolph AM. Oxygen uptake in infants and children: as simple method for measurement. *Pediatrics* 1974;53:656-62.
- 16 Nakazawa M, Takao A, Shimizu T, Chon Y. Afterload reduction treatment for large ventricular septal defects. Dependence of haemodynamic effects of hydralazine on pretreatment systemic blood flow. *Br Heart J* 1983;49:461-5.
- 17 Beekman RH, Rocchini AP, Rosenthal A. Hemodynamic effects of nitroprusside in infants with a large ventricular septal defect. *Circulation* 1981;64:553-8.
- 18 Berisha S, Kastrati A, Kondili A, Popa Y, Goda A. Trajtimi me nitroprusid te natriumit i ruptures akute te septumit ventrikular gjate infarktut akut te miokardit. *Revista Mjekesore* 1986;4:37-41.
- 19 Rudolph AM, Nadas AS. The pulmonary circulation and congenital heart disease. Considerations of the role of the pulmonary circulation in certain systemic-pulmonary communications. *N Engl J Med* 1962;267:968-74.
- 20 Schrire V, Vogelpoel L, Beck W, Nellen M, Swanepoel A. Ventricular septal defect: the clinical spectrum. *Br Heart J* 1965;27:813-28.
- 21 Collins G, Calder L, Rose V, Kidd L, Keith J. Ventricular septal defect: clinical and hemodynamic changes in the first five years of life. *Am Heart J* 1972;84:695-9.
- 22 Lupi-Herrera E, Sandoval J, Seoane M, Bialostozky D. The role of hydralazine therapy for pulmonary arterial hypertension of unknown cause. *Circulation* 1982;65:645-50.
- 23 Fripp RR, Gewitz MH, Werner JC, Whitman V, Rashkind WJ. Oral hydralazine in patients with pulmonary vascular disease secondary to congenital heart disease. *Am J Cardiol* 1981;48:380-2.
- 24 Rubin LJ, Nicod P, Nillis LD, et al. Treatment of primary pulmonary hypertension with nifedipine: a hemodynamic and scintigraphic evaluation. *Ann Intern Med* 1983;99:433-8.
- 25 Levin AR, Klein AA, Reidenberg MM, Engle MA. Effects of vasodilators on left to right shunts in infants and children [Abstract]. *Pediatr Res* 1980;14:447.