Acute haemodynamic effects of nifedipine in patients with ventricular septal defect

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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. Their beneficial effects are more pronounced in the congestive heart failure secondary to valvar regurgitation and to mechanical complications of acute myocardial infarction. 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.

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. Opposite effects were seen with vasopressor drugs.

Clinical studies in patients with ventricular septal defect and congestive heart failure confirmed these data.

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
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 resistance from 1076.5 (185.2) to 970.2 (150.4) dyn.s.cm⁻¹ (p = 0.04). The pulmonary vascular resistance was not significantly affected by nifedipine administration (p = 0.16).

**Group B**

Nifedipine administration did not significantly affect the mean aortic and pulmonary arterial pressures or the pulmonary vascular resistance. However, the systemic vascular resistance was significantly reduced (p = 0.03).
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Fig 1  Effect of nifedipine on systemic blood flow in patients with ventricular septal defect and pulmonary hypertension (group B). C, control; N, nifedipine; Qs, 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/Qs, pulmonary to systemic flow ratio.

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.
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 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) versus 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) versus 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).
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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. These changes were dependent upon the extent to which systemic vascular resistance was reduced, as shown by another study of nitrates. Experimental studies of ventricular septal defect showed that the amount of interventricular shunting was largely determined by the left ventricular afterload. The left to right shunt was increased by the infusion of pressor amines and reduced (by 33%) after α blockade with phentolamine and phenoxybenzamine. A considerable decrease was seen after hydralazine administration and even more with prazosin. In clinical studies too hydralazine significantly increased the systemic blood flow in patients with a large ventricular septal defect. 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. In other studies these measurements did not change or changed in only some cases. Indeed there are reports of a significant increase in pulmonary to systemic flow ratio and systemic vascular resistance in response to these agents. 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, the values of systemic and pulmonary vascular resistance, and in particular the left ventricular preload and performance.

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 performance 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. 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 amines and lowered by decreasing the raised systemic vascular resistance with vasodilators. 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 ratio; 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.

Vasodilator drugs dilate the systemic and pulmonary vascular bed in patients with congestive heart failure of various aetiologies. Their effect in the pulmonary circulation is not, however, constant. Nifedipine and other vasodilators do not always succeed in lowering pulmonary vascular resistance; indeed in other studies an increase has been seen. 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 and hydralazine. 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. 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. 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%).

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
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