

Mechanisms of blood pressure increase induced by dopamine in hypotensive preterm neonates

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Abstract

Aims—To compare changes in global haemodynamics as well as anterior cerebral and superior mesenteric artery perfusion after dopamine treatment.

Methods—Anterior cerebral and superior mesenteric artery perfusion was measured using Doppler ultrasonography in hypotensive preterm neonates in whom cardiac output increased (group 1, n=10) or decreased (group 2, n=40) after dopamine treatment.

Results—Despite a lower dopamine infusion rate, the blood pressure increase (mm Hg) in group 2 [$\Delta=13(1)$; mean(SE)] exceeded that in group 1 [$\Delta=8(1)$], while systemic vascular resistance (mm Hg/l/min/kg) rose in group 2 [$\Delta=106(37)$], but was unchanged in group 1 [$\Delta=9(6)$]. Anterior cerebral artery blood velocity and resistance were unaffected by dopamine. However, compared with unchanged values in group 1, superior mesenteric artery blood velocity fell by 14.7(4.8) cm/s and resistance increased by 4.1(0.7) mm Hg/cm in group 2.

Conclusions—These results suggest that, in a portion of hypotensive preterm neonates, the increase in blood pressure induced by dopamine is related to a predominant vasoconstrictor action and is associated with a fall in bowel perfusion.

(Arch Dis Child Fetal Neonatal Ed 1999;81:F99–F104)

Keywords: dopamine; hypotension; preterm infants

Around 20% of preterm infants admitted to neonatal intensive care units become hypotensive within 24 hours of admission.¹ Because hypotension in preterm infants has been linked to the subsequent development of deleterious consequences, such as cerebral ischaemia and haemorrhage,^{2–5} and necrotising enterocolitis,⁶ the emergence of this complication requires prompt corrective treatment. The current recommended treatment for hypotension in preterm neonates is initial volume expansion with colloid solution, followed by infusion of an inotropic agent in those neonates who are unresponsive to volume loading.⁷

An inotropic agent commonly used in preterm neonates for the treatment of hypotension refractory to volume loading is dopamine, a catecholamine with β -adrenoceptor mediated inotropic and α -adrenoceptor mediated vasoconstrictor actions, as well as peripheral vasodilatory effects arising from stimulation of dopaminergic receptors.⁸ A considerable number of clinical^{9–15} and experimental^{14,15}

studies have attested to the efficacy of dopamine in raising blood pressure in neonates. However, this agent has been reported to both increase^{9,16} and reduce cardiac output.¹¹ Although the basis of this variable cardiac output response has not been fully elucidated, one possibility is that increases in cardiac output reflect a predominant inotropic action, whereas reductions in cardiac output are primarily a manifestation of the vasoconstrictor effects of dopamine. If this were indeed the case, then the nature of cardiac output changes elicited by dopamine may have important implications for the perfusion of vital organs such as the brain and intestine.

Accordingly, this study aimed to compare haemodynamic changes in hypotensive neonates in whom left ventricular output, assessed from Doppler echocardiographic measurements of ascending aortic blood flow, increased or decreased after dopamine treatment. Secondly, the study aimed to evaluate dopamine induced alterations in cerebral and intestinal perfusion in the same infants using Doppler ultrasonographic assessment of anterior cerebral and superior mesenteric arterial blood velocities, respectively.

Methods

The study was undertaken in accordance with guidelines established by the National Health and Medical Research Council of Australia, and approved by the Monash Medical Centre Human Ethics Committee. Informed consent was obtained from the parent or legal guardian prior to enrolment of neonates in the study.

STUDY PROTOCOL

The study group was performed in 14 very low birthweight neonates admitted to the neonatal intensive care unit at Monash Medical Centre with respiratory distress, who subsequently developed hypotension between 1 and 30 hours after birth. All neonates were less than 32 weeks of gestation (range 24 to 31 weeks), with birthweights ranging from 480 to 1482 g, and who were on assisted ventilation at the time of the study.

Blood pressure was monitored continuously through a peripheral arterial or an umbilical arterial catheter, using a multichannel neonatal monitor (HP 78A, Hewlett Packard, USA). Hypotension, defined as a mean arterial pressure (MAP) \leq 10th percentile of the normal range, taking account of birthweight and postnatal age,⁴ was present in all neonates and was initially treated with volume therapy using either one (n = 12) or two courses (n = 2) of 10 ml/kg of 4% human albumin (CSL

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Accepted 3 May 1999

Limited, Australia). Patients in the study group were deemed by the treating physician not to have responded to volume loading and were therefore given inotropic support with dopamine. Once the decision to administer dopamine was made, all neonates underwent a baseline ascending aortic, anterior cerebral artery, and superior mesenteric artery Doppler ultrasonographic study. Dopamine (David Bull Laboratories, Australia) was administered as a continuous infusion via a peripheral venous catheter or a central venous line (Adult/ Neonatal Syringe Pump 1235, Atom Medical Corp., Japan). The infusion rate of dopamine, which was at the discretion of the treating doctor, ranged between 5 and 10 $\mu\text{g}/\text{kg}/\text{min}$ and was chosen on the basis of the clinical status of the patient. This infusion rate was maintained until completion of a repeat Doppler ultrasonographic study, which was performed after MAP had increased to a steady state level within the normal range, 30–80 minutes after the initiation of dopamine treatment. Infants did not develop any cardiac arrhythmia related to dopamine treatment. Baseline arterial blood gas variables (pH: mean (SE) 7.34(0.03)), pO_2 : 59(4) mm Hg, pCO_2 : 39(4) mm Hg, base excess: -4.9 (0.7) mmol/l) were unchanged during dopamine infusion (mean (SE) difference = -0.01 (0.03), 4(5), 2(4), and 0.1(0.6), respectively). No other drugs with a potential impact on blood pressure or vascular tone were given during dopamine administration.

DOPPLER ULTRASONOGRAPHY

Doppler echocardiographic evaluations were performed with neonates in a supine position, using a Sonos 1000 (Hewlett Packard, USA) ultrasound imaging system and a 7.5 MHz

transducer. All studies were recorded on video tape at a speed of 100 mm/s for later review and off-line analysis by a single observer (JZ).

After normal cardiac anatomy had been established using cross sectional echocardiography, the left ventricular outflow tract was imaged with two dimensional echocardiography using an apical view which incorporated the full length of the ascending aorta. The pulsed Doppler sample volume was placed in the ascending aorta immediately distal to the aortic valve, and the blood velocity–time signal was recorded, keeping the angle of incidence of the ultrasound beam with the blood flow vector between 0° and 20° .¹⁷ To obtain internal diameter, the ascending aorta was imaged with M-mode echocardiography in the parasternal long axis view.^{18,19} The ductus arteriosus was imaged using a short axis view of the right ventricular outflow tract,²⁰ and ductal size, direction of flow, and haemodynamic importance assessed using two dimensional echocardiography and colour Doppler imaging. An electrocardiogram was simultaneously recorded during cardiac echocardiography.

For the cerebral perfusion study, the anterior cerebral artery was imaged through the anterior fontanelle at its curvature around the corpus callosum, where the angle of insonation is close to 0° .¹² For the intestinal perfusion study, Doppler ultrasonography was performed on the superior mesenteric artery via a longitudinal abdominal approach. The sample volume was placed just distal to the origin of the superior mesenteric artery from the aorta, which corresponded to an angle of insonation of 0 – 15° .²¹ At both sites, the presence of maximal amplitude blood flow velocity wave forms was verified by acoustic and visual control of the spectral display.

Table 1 Demographic data and dopamine infusion rate in neonates with an increase (group I) or fall (group II) in cardiac output after dopamine

	Group 1 (n = 10)	Group 2 (n = 4)	p Value
Birthweight (g)	967 (74)	930 (187)	0.8
Gestational age (weeks)	27 (0.7)	26 (1.7)	0.5
Age at time of study (hours)	11 (3)	19 (6)	0.2
Apgar score			
1 min	4 (1)	4 (1)	0.9
5 mins	8 (0.2)	7 (0.8)	0.3
CRIB score	5.4 (1.2)	7.0 (2.4)	>0.5
Arterial:alveolar O_2 tension ratio	0.20 (0.03)	0.19 (0.05)	0.8
Blood urea (mmol/l)	4.9 (1.3)	5.1 (1.1)	>0.9
Diameter of ductus arteriosus (mm)	2.9 (0.2)	2.8 (0.5)	0.8
Ductus arteriosus shunt			
left to right	40%	50%	>0.9
bidirectional	60%	50%	>0.9
Dopamine infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	8 (1)	6 (1)	<0.05

Values are expressed as mean (SE).

Table 2 Baseline hemodynamic data in neonates with an increase (Group 1) or fall (Group 2) in cardiac output after dopamine therapy

	Group 1 (n = 10)	Group 2 (n = 4)	p Value
Mean blood pressure (mm Hg)	26 (1)	24 (2)	0.2
Heart rate (beats/min)	148 (7)	149 (4)	0.9
Left ventricular output (ml/min/kg)	205 (25)	218 (43)	0.8
Systemic vascular resistance (mm Hg/l/min/kg)	150 (25)	127 (33)	0.6
Anterior cerebral mean blood velocity (cm/s)	10.3 (1.6)	9.7 (1.9)	0.8
Anterior cerebral flow velocity–time integral (cm)	4.3 (0.8)	4.1 (0.8)	0.9
Anterior cerebral resistance index (mm Hg/cm)	7.4 (0.8)	6.6 (1.4)	0.6
Superior mesenteric mean blood velocity (cm/s)	23.9 (2.8)	31.7 (6.6)	0.2
Superior mesenteric flow velocity–time integral (cm)	9.8 (1.4)	12.3 (2.8)	0.4
Superior mesenteric resistance index (mm Hg/cm)	3.0 (0.4)	2.4 (0.5)	0.2

Values are expressed as mean (SE).

MEASUREMENTS AND CALCULATIONS

The severity of respiratory distress in the preterm neonates was assessed using the arterial:alveolar O_2 tension ratio. The alveolar O_2 tension was calculated as $713 \cdot \text{FIO}_2 - [\text{PaCO}_2/\text{R}]$ where FIO_2 was the inspired O_2 concentration, R, the respiratory quotient, which was assumed to equal 1, and PaCO_2 , the arterial CO_2 tension in mm Hg.²²

Heart rate was calculated from the R-R interval of the electrocardiogram. The velocity–time integral of the ascending aorta was obtained by planimetry and averaged over three to five consecutive cardiac cycles. The internal diameter of the ascending aorta (AOD) was measured at the end of systole^{18,19} and averaged over three to five cardiac cycles. Left ventricular output (ml/min/kg) was then calculated as $[\pi \cdot (\text{AoD})^2 / 4] \cdot \text{velocity–time integral} \cdot \text{heart rate} / \text{body weight}$,¹⁹ while systemic vascular resistance was computed as $\text{MAP} / \text{left ventricular output}$ and expressed as mm Hg/l/min/kg.

The mean velocity (cm/s) and velocity–time integral (cm) of the anterior cerebral and superior mesenteric arteries were obtained by planimetry and averaged over five consecutive cycles. The resistance index for each site was

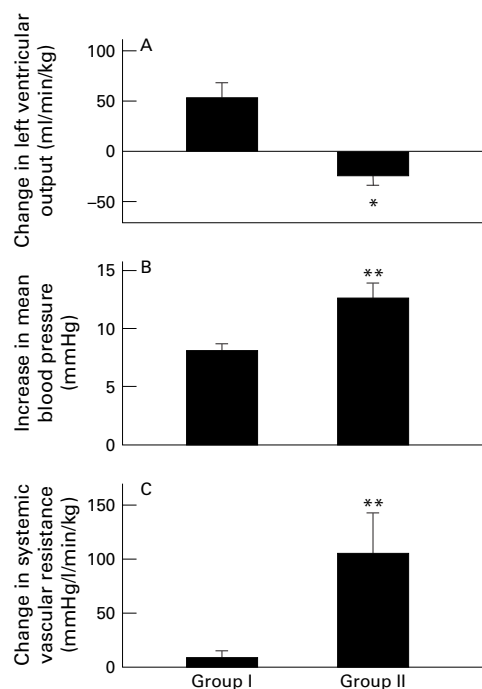


Figure 1 Change in left ventricular output (A), mean blood pressure (B), and systemic vascular resistance (C) after dopamine treatment in groups 1 and 2 neonates. Values are expressed as mean (SE): * $p < 0.05$; ** $p < 0.01$, group 1 vs group 2

calculated as $\text{MAP} / \text{velocity-time integral}$ and expressed as mm Hg/cm.

STATISTICAL ANALYSIS

Infants were allocated into two groups on the basis of whether their left ventricular output increased (group 1, $n = 10$) or fell (group 2, $n = 4$) with dopamine treatment, and other haemodynamic, blood gas, and ultrasonographic data were analysed accordingly. Data before and after dopamine were compared using a paired t test if normally distributed or a Wilcoxon sign-rank test if not normally distributed, while unpaired data were compared with one way analysis of variance.²³ All data are reported as the mean (SE) and statistical significance was taken as $p < 0.05$.

Results

Birthweight, gestational age, age at the time of study, Apgar scores at birth, clinical risk index for babies (CRIB) score,²⁴ blood urea, the arterial:alveolar oxygen tension ratio and the diameter of the ductus arteriosus were not significantly different between the two study groups, but the dopamine infusion rate was higher in group 1 neonates (table 1). Ductal flow was present in all neonates, with a similar proportion of left-to-right and bidirectional shunting in the two groups. However, because it occurred only in diastole, was of low velocity, and was not associated with atrial or ventricular enlargement, ductal shunting was not considered to be haemodynamically significant in any neonate. Baseline mean arterial blood pressure, left ventricular output, heart rate and systemic vascular resistance, as well as the anterior cerebral and superior mesenteric

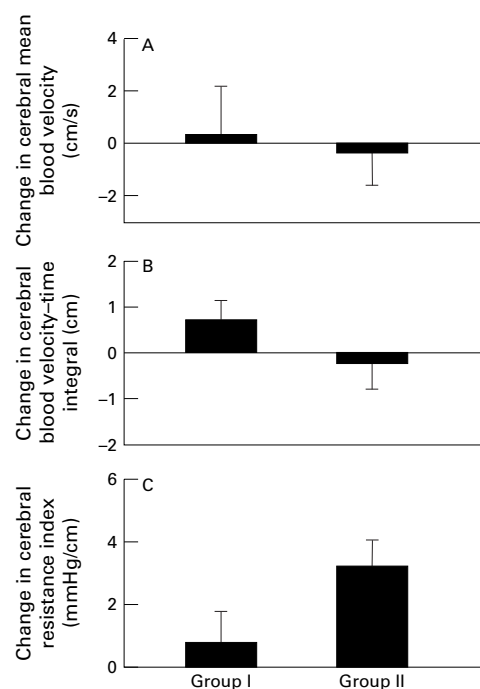


Figure 2 Changes in anterior cerebral artery mean blood velocity (A) and blood velocity-time integral (B), and cerebral vascular resistance index (C) after dopamine treatment in both groups.

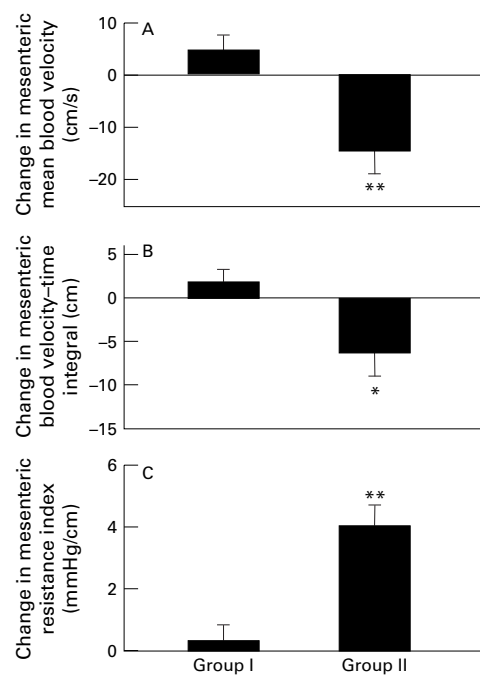


Figure 3 Change in mesenteric artery mean blood velocity (A) and blood velocity-time integral (B) and mesenteric resistance index (C) after dopamine treatment in both groups: * $p < 0.05$; ** $p < 0.01$, group 1 vs group 2.

artery mean blood velocities, velocity-time integrals and resistance indices were not significantly different between the two groups (table 2).

In association with the differing left ventricular output response to dopamine (fig 1A), the increase in MAP was significantly lower in group 1 [$\Delta = 8(1)$ mm Hg] compared with group 2 infants [$\Delta = 13(1)$ mm Hg]; $p < 0.01$ (fig 1B). Moreover, compared with the

Table 3 Clinical outcome in neonates with an increase (group 1) or fall (group 2) in cardiac output after dopamine

Outcome	Group 1 [n = 10]	Group 2 [n = 4]	p Value
Survival with no major complication	4	3	0.6
Survival complicated by			
- necrotising enterocolitis	2	0	>0.9
- cerebral haemorrhage	1	0	>0.9
Death	3	1	>0.9

unchanged systemic vascular resistance in group 1 neonates [$\Delta = 9(6)$ mmHg/l/min/kg], this variable rose in group 2 neonates [$\Delta = 106(37)$ mmHg/l/min/kg]; $p < 0.01$ (fig 1C). Changes in heart rate were not significantly different between group 1 [$\Delta = 8(5)$ beats/min] and group 2 infants [$\Delta = 2(3)$ beats/min]; $p = 0.4$.

The anterior cerebral artery mean blood flow velocity, velocity–time integral, and resistance index were unaffected by dopamine and were not significantly different between the groups (fig 2). However, compared with the unchanged mean blood flow velocity [$\Delta = 4.8(2.9)$ cm/s], velocity–time integral [$\Delta = 1.7(1.3)$ cm], and resistance index [$\Delta = 0.4(0.5)$ mm Hg/cm] of the superior mesenteric artery in group 1 infants, mean blood flow velocity fell by 14.7(4.8) cm/s; $p < 0.01$ (fig 3A), and velocity–time integral by 6.4(2.7) cm; $p < 0.05$ (fig 3B), while the resistance index increased by 4.1(0.7) mm Hg/cm; $p < 0.005$ (fig 3C) in the superior mesenteric artery of group 2 infants.

With the relatively small number of neonates in the study, no significant difference was detectable in the outcome of both groups of infants (table 3). The cause of death in both subgroups was primarily respiratory in origin, although one group 1 neonate had a concurrent severe cerebral haemorrhage.

Discussion

The rationale for administration of dopamine in hypotensive preterm neonates unresponsive to volume therapy is to increase systemic perfusion pressure, and thereby systemic blood flow and oxygen delivery. However, the results of this study suggest that, in this setting, dopamine induced increases in arterial blood pressure may be underpinned by two distinct processes. Thus the combination of a rise in blood pressure with an increase in left ventricular output and an unchanged systemic vascular resistance observed in group 1 neonates was consistent with a primarily inotropic effect. On the other hand, the combination of an increase in blood pressure with a reduction in left ventricular output and a rise in systemic vascular resistance apparent in group 2 infants was highly suggestive of a predominant vasoconstrictor action of dopamine.

The differing cardiac output responses to dopamine observed in these neonates were not related to differences in the baseline level of left ventricular output,⁹ the extent of patency or shunting via the ductus arteriosus,²⁵ or the baseline arterial:alveolar O₂ tension ratio.¹¹ Furthermore, although it is well recognised

that dopamine has vasodilatory and inotropic effects at an infusion rate of <10 $\mu\text{g}/\text{kg}/\text{min}$ and vasoconstrictor effects at >10 $\mu\text{g}/\text{kg}/\text{min}$ in adults,²⁶ the difference in observed cardiac output responses in preterm infants was not simply due to such a dose related phenomenon. Specifically, the average dopamine infusion rate was less than 10 $\mu\text{g}/\text{kg}/\text{min}$ for both groups; but not only was the infusion rate in neonates with a reduced cardiac output lower than in infants with an increased cardiac output, but it resulted in a greater rise in arterial blood pressure (table 1). Taken together, the foregoing features are consistent with a predominance of the vasoconstrictor effects of dopamine in a proportion of preterm infants in the immediate period after birth.

At least three factors prevalent in the initial days after birth are likely to have predisposed to the manifestation of the vasoconstrictor actions of dopamine in some infants of our study. First, experimental studies have indicated that β -adrenoceptor mediated inotropic responses to dopamine in neonatal myocardium are less pronounced than in adults,²⁷ an effect which may in part arise because of a lower density of β -adrenoceptors.²⁸ In addition, an indirect inotropic action, which is due to dopamine induced release of noradrenaline from myocardial sympathetic nerve terminals,²⁶ is not prominent in preterm infants,⁹ presumably because of an immaturity of cardiac sympathetic innervation.²⁹

The second factor which probably facilitated the vasoconstriction actions of dopamine in preterm infants is the high density of α -adrenoceptors apparent during fetal development and in the initial period after birth.²⁸ Consistent with this proposition, dopamine induced rises in blood pressure in one day old piglets were associated with rises in renal, femoral, and carotid arterial vascular resistance, which was abolished by α -adrenergic blockade.³⁰ The final factor that may have promoted the vasoconstrictor actions of dopamine in preterm infants is that the vasodilation mediated by dopaminergic receptors is incompletely developed in the immediate neonatal period.^{30 31}

An important consideration in the administration of dopamine to hypotensive preterm infants is its effect on the perfusion of vital organs such as the brain and intestine. Our observation that anterior cerebral artery blood velocities and resistance indices did not change significantly in both groups of infants suggests that cerebral perfusion was maintained, irrespective of whether dopamine increased or reduced cardiac output. On the other hand, while superior mesenteric artery blood velocities and resistance indices were unaltered in group 1 infants, blood flow velocity was reduced and resistance was increased in this vessel in group 2 infants. As the superior mesenteric artery supplies the entire bowel except for the superior part of the duodenum and distal part of the colon,³² the latter finding is indicative of a reduction in bowel perfusion.

On the basis of these data, we are unable to distinguish between two mechanisms which

could account for the preservation of cerebral, but reduction in intestinal, perfusion in group 2 infants. The first relates to the presence of fewer vasoconstrictor α -adrenoceptor and/or more vasodilator dopaminergic receptors in the cerebral vasculature. The second involves a greater capacity of autoregulatory mechanisms in the cerebral vasculature to counteract any α -adrenoceptor mediated vasoconstriction induced by dopamine. However, consistent with a role for the latter mechanism, experiments in piglets suggest that intestinal autoregulation does not appear until several weeks after birth,³³ whereas cerebral autoregulation is detectable in roughly half of preterm infants ≤ 32 weeks of gestation in the initial days after birth.³⁴

An inherent limitation of the cerebral and intestinal Doppler ultrasonographic arms of our study was that changes in perfusion were assessed from alterations in blood velocity instead of blood flow. Although Doppler ultrasonography can provide excellent visualisation of the anterior cerebral and superior mesenteric arteries for precise placement of the Doppler sample volume and subsequent measurement of blood velocity, the small internal diameter of these vessels in preterm infants (<2 mm) precludes an accurate assessment of associated changes in vessel dimensions during infusion of vasoactive drugs.³⁵ It is therefore possible that, particularly with the superior mesenteric artery, reductions in measured blood velocities underestimated the magnitude of the actual fall in intestinal blood flow.

On the basis of the present data, it is difficult to draw any firm conclusions about the relation between the nature of dopamine induced changes in global or regional perfusion and neonatal outcome, in terms of either morbidity or mortality. Thus while superior mesenteric vasoconstriction was observed in group 2 infants, two cases of necrotising enterocolitis occurred in group 1 infants. Similarly, two instances of cerebral haemorrhage were observed in group 1 neonates. Furthermore, the mortality was similar in group 1 (30%) and group 2 infants (25%). This aspect of our study is clearly limited not only because of our small patient numbers, but also because the pathogenesis of necrotising enterocolitis and cerebral haemorrhage is often multifactorial,^{2-6 36 37} yet outcomes in this study were only assessed in relation to global and regional perfusion responses after the initial administration of dopamine.

In summary, our results suggest that the increase in blood pressure induced by dopamine in hypotensive preterm neonates may be related to either a predominant inotropic or vasoconstrictor action of this agent. Doppler ultrasonographic measurement of cardiac output or superior mesenteric blood velocity before and after dopamine infusion may assist in the discrimination between these actions. Although no link was demonstrable between the nature of the haemodynamic response to dopamine and neonatal outcome in our small study group, further investigation is required to establish if it may be more appropriate to use an alternative agent in the

subgroup of preterm neonates displaying a vasoconstrictor response to dopamine.

We thank the medical and nursing staff of the Newborn Services Unit at Monash Medical Centre for their assistance in carrying out this study.

This study was performed with the assistance of a Grant-in-Aid from the National Heart Foundation of Australia.

Dr J Zhang was supported by a postgraduate scholarship from the University of Queensland.

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