Response to dobutamine and dopamine in the hypotensive very preterm infant

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Abstract
A randomised double blind study was designed to evaluate haemodynamic response to dobutamine and dopamine in 20 hypotensive preterm infants of less than 32 weeks' gestation. Neonates initially received dopamine or dobutamine 5 μg/kg/min. If mean arterial pressure (MAP) remained below 31 mm Hg, the infusion rate was increased in increments of 5 μg/kg/min. If 20 μg/kg/min of the initial drug failed to achieve a MAP above 30 mm Hg, it was discontinued and the other drug was administered at the same infusion rate. Left ventricular output (LVO) was measured by pulsed Doppler echocardiography.

Mean (SE) MAP increased significantly from 24·4 (1·0) to 32·0 (1·4) mm Hg at a median dobutamine dosage of 20 μg/kg/min and from 25·6 (1·2) to 37·7 (1·5) mm Hg at a median dopamine dosage of 12·5 μg/kg/min. The percentage LVO increase was +21 (7)% with dobutamine compared with −14 (8)% with dopamine. Dobutamine failed to increase MAP above 30 mm Hg in six infants out of 10, whereas dopamine succeeded in all 10 infants. Six switches from dobutamine to dopamine were thus performed, providing a rise in MAP (29·2 (0·5) to 41·2 (2·0) mm Hg) and drop in LVO (356 (40) to 263 (36) ml/kg/min). These data indicate that dopamine is more effective than dobutamine in raising and maintaining MAP above 30 mm Hg; however dopamine does not increase LVO.
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Cerebral ischaemic lesions are among the major complications of extreme prematurity. Mean arterial pressure (MAP) below 30 mm Hg precedes such lesions[1][2] and requires the use of inotropic drugs to increase or maintain MAP above 30 mm Hg.[3] The drugs conventionally used are dopamine and dobutamine, each of which has certain advantages and disadvantages. Dopamine is the drug most often used by neonatalogists,[4] although the predominance of its alpha effect during the neonatal period,[5] may induce two risk factors: (i) increase in left ventricular afterload and decrease in heart output[6][7] and (ii) increased pulmonary resistance associated with a risk of persistent neonatal pulmonary hypertension.[8][9] Theoretically, the beneficial effect of dobutamine is due to its essential β adrenergic action. Its inotropic effect has been demonstrated also in preterm neonates,[10] but its ability to increase MAP seems to be more restricted, according to studies in adults[11] or young children.[12] As few controlled studies on the haemodynamic effects of these two drugs in the very preterm neonate have been reported, we designed a randomised double blind prospective study to analyse haemodynamic response to each drug within a population of hypotensive preterm infants born at less than 32 weeks' gestation.

Patients and methods
PATIENTS
Institutional approval was obtained for this study. All neonates born before 32 weeks' gestation and admitted to the neonatal intensive care unit of Nantes University Hospital during two periods, from 1 January to 30 September 1990 and from 15 April to 30 September 1992, were eligible. Several conditions had to be met: (i) infants had to present with a MAP below 30 mm Hg for more than one hour despite vascular fill with 20 ml/kg albumin 4%, (ii) infants had to be able to undergo Doppler echocardiographic examination before and during infusion of a positive inotropic drug, and (iii) informed consent had to be obtained from the parents.

DRUG ADMINISTRATION
Neonates included in the study were randomised to either dobutamine or dopamine and received a continuous infusion of dobutamine or dopamine at an initial dose of 5 μg/kg/min. Whenever MAP could not be maintained above 30 mm Hg, the dose was increased in increments of 5 μg/kg/min up to a maximum dose of 20 μg/kg/min. When that dose failed, a switch was made to the other drug, with infusion at the same 20 μg/kg/min dose. If MAP could not be maintained above 30 mm Hg after the switch, the subject was withdrawn from the protocol. Drugs were prepared and administered by nurses. Each drug was diluted down to 1000 μg/ml. The medical team was unaware of randomisation results and prescribed the dosage by adapting the infusion rate.

DATA ANALYSIS AND MEASUREMENTS
The severity of respiratory distress was determined from the arterial alveolar oxygen tension ratio (a/AO$_2$), PAO$_2$ being computed according

Table 1   Clinical characteristics of the study group

Patient No	Weight (g)	Term (weeks)	a/Ao₂*	MAP monitoring	Drug	Maximum dosage (µg/kg/min)	MAP >30 mm Hg	Follow up by day 28
1	1300	27	0·47	Arterial catheter	Dobutamine	20	No	BPD, PVL
2	1160	29	0·21	Oscillometric	Dobutamine	10	Yes	PVL
3	1200	30	0·14	Arterial catheter	Dobutamine	20	No	BPD
4	980	27	0·38	Oscillometric	Dobutamine	20	Yes	Normal
5	1080	30	0·15	Oscillometric	Dobutamine	20	No	Normal
6	1100	28	0·16	Oscillometric	Dobutamine	20	No	PVL
7	810	29	0·13	Arterial catheter	Dobutamine	20	No	Non-survivor
8	700	26	0·36	Arterial catheter	Dobutamine	20	No	Non-survivor, NEC
9	1660	31	0·29	Arterial catheter	Dobutamine	5	Yes	Normal
10	1090	29	0·33	Oscillometric	Dobutamine	15	Yes	Normal
11	800	31	0·41	Oscillometric	Dopamine	20	Yes	Normal
12	1400	31	0·32	Oscillometric	Dopamine	15	Yes	Normal
13	1800	31	0·19	Oscillometric	Dopamine	10	Yes	Non-survivor (PPHN)
14	1300	27	0·12	Arterial catheter	Dopamine	5	Yes	Non-survivor
15	1200	27	0·30	Arterial catheter	Dopamine	20	Yes	Normal
16	1200	30	0·20	Oscillometric	Dopamine	5	Yes	PVL
17	670	28	0·08	Arterial catheter	Dopamine	15	Yes	BPD
18	880	29	0·18	Oscillometric	Dopamine	10	Yes	Normal
19	900	27	0·20	Arterial catheter	Dopamine	15	Yes	BPD
20	1220	29	0·25	Arterial catheter	Dopamine	5	Yes	Non-survivor, PVL+IVH

*a/Ao₂: arterial alveolar oxygen tension ratio on entry to trial.
BPD: bronchopulmonary dysplasia; PVL: periventricular leucomalacia; IVH: intraventricular haemorrhage;
PPHN: persistent pulmonary hypertension of the newborn; NEC: necrotising enterocolitis.

to the formula: $PAo_2=713 \times FIo_2-(PaCo_2/R)$, where R=1, PaO_2 and $PaCO_2$ being expressed as mm Hg.[13] MAP measurements were determined by using either a 3·5 French umbilical artery catheter connected to a pressure transducer (model 60-800, American Edwards Laboratories) via a low compliance tube,[14] or the non-invasive oscillometric method (Dynamap 1846, Critikon Inc). Cuff width on the upper right arm was carefully chosen to minimise errors.[15] Left ventricular output (LVO) was measured by duplex echocardiography (Ultramark 5, Advanced Technology Laboratories). Doppler echocardiographic examination using a 7·5 MHz scanner and a 5 MHz Doppler probe was performed before drug administration, upon delivery of the highest infusion rate delivered, and after the switch if it occurred. The examination included M mode measurement of the end systolic internal diameter of the ascending aorta.[16-18] Measured at the first examination, this diameter was considered to be constant throughout the study. Variation in aortic diameter between measurements was probably due to methodological error or limitations rather than to true changes with time in aortic diameter.[17] Mean velocity was measured on five consecutive cycles in the ascending aorta, through either the suprasternal or subcostal views. The angle of incidence of the ultrasound beam with the blood flow vector was kept between 0±15 degrees. LVO was determined by multiplying the aortic section area, computed from M mode measured diameter, by mean velocity divided by birth weight in order to express LVO in ml/min/kg.[17] Systemic vascular resistance (SVR), estimated by dividing MAP by LVO and body area, was expressed as dynes×sec/cm⁵/m².[19]

STATISTICAL ANALYSIS

Results are reported as mean (SE). Fisher's exact test (two tailed) was used to compare the ability of both drugs to increase MAP above 30 mm Hg. The Wilcoxon paired test and the Kruskal-Wallis test were used to compare variations in haemodynamic parameters respectively within and between groups. A simple linear regression was performed. A p<0·05 threshold was considered as statistically significant.

Results

Twenty preterm infants were enrolled in the study: 10 in the dobutamine group and 10 in the dopamine group (see table 1 for clinical data). No patients were withdrawn from the study. Infants in both groups were not statistically different for birth weight (1110 (80) v 1140 (105) g) or gestational age (28·7 (0·5) v 29·0 (0·5) weeks). All 20 neonates were receiving assisted ventilation. The severity of the respiratory distress was not statistically different between both groups. The mean a/Ao₂ ratio upon inclusion was 0·26 (0·04) in the dobutamine group compared with 0·23 (0·03) in the dopamine group; this was not significant.

MAP changes in both groups at different dosages are indicated in fig 1. MAP increased significantly in both groups, from 24·4 (1·0) to 32·0 (1·4) mm Hg (p=0·0006) at a median dosage of 20 µg/kg/min in the dobutamine group and from 25·6 (1·2) to 37·7 (1·5) mm Hg (p=0·0002) at a median dosage of 12·5 µg/kg/min in the dopamine group. MAP increased above 30 mm Hg for all 10 hypotensive neonates receiving dopamine, but remained at or below 30 mm Hg for six of the 10 neonates receiving dobutamine, even at a 20 µg/kg/min dose.

The difference between LVO before drug administration and on the maximum dose was +21 (7)% for the dobutamine group compared with −14 (8)% for the dopamine group (p=0·005). In the dopamine group, we observed a significant positive correlation between a/Ao₂ on entry to the trial and the difference between LVO before dopamine administration and at the highest infusion rate of dopamine (r=0·71, n=10, p=0·02; fig 2). The difference between SVR before drug administration and on the maximum dose was

Table 2 Comparison of haemodynamic effects of dobutamine and dopamine. Changes in MAP, LVO, and SVR measured before treatment and at the highest infusion rate. Results are mean (SE)

	Dobutamine (n=10)		Dopamine (n=10)	
	Before treatment	Highest infusion rate	Before treatment	Highest infusion rate
Dosage (μg/kg/min)		17·0 (1·7)		12·0 (1·8)
MAP (mm Hg)	24·4 (1·0)*	32·0 (1·4)†	25·6 (1·2)*	37·7(1·5)†
LVO (ml/min/kg)	269 (36)	313 (37)†	245 (23)	206 (21)†
SVR (dynes/sec/cm⁵/m²)	1035 (188)	1171 (237)†	1124 (186)*	1952 (300)†

*p<0·026 between parameters measured before treatment and at the highest infusion rate, within dobutamine or dopamine groups.
†p<0·024 between dobutamine or dopamine groups at the highest infusion rate.

+14 (13)% for the dobutamine group and +92 (28)% for the dopamine group (p=0·02). The increase in heart rate was similar in both groups (+15 (5)% for dobutamine and +8 (4)% for dopamine). Variations between MAP, LVO, and SVR data before treatment and at the highest infusion rate are shown in table 2. No failures were observed in the 10 infants on dopamine, whereas six of the 10 on dobutamine failed (p=0·01), requiring six switches from dobutamine to dopamine.

After these six switches from 20 μg/kg/min of dobutamine to the same dose of dopamine, MAP increased from 29·2 (0·5) to 41·2 (2) mm Hg (p=0·005), SVR increased from 837 (86) to 1703 (310) dynes×sec/cm⁵/m² (p=0·02), and LVO decreased from 356 (40) to 263 (36) ml/min/kg (not significant). The individual variations in MAP, LVO, and SVR during the six switches are indicated in fig 3. In total, 16 hypotensive infants received dopamine infusion (10 at the beginning and six after a switch from dobutamine). MAP rose above 30 mm Hg in 16/16 infants on dopamine compared with 4/10 on dobutamine (p=0·0009).

Discussion

Our results show that dopamine was more effective than dobutamine in increasing MAP above 30 mm Hg in hypotensive preterm neonates. The dopamine increase was secondary to an increase in SVR but not in LVO, whereas dobutamine increased cardiac output but had a lesser effect on MAP. The effects of dopamine during the neonatal period, as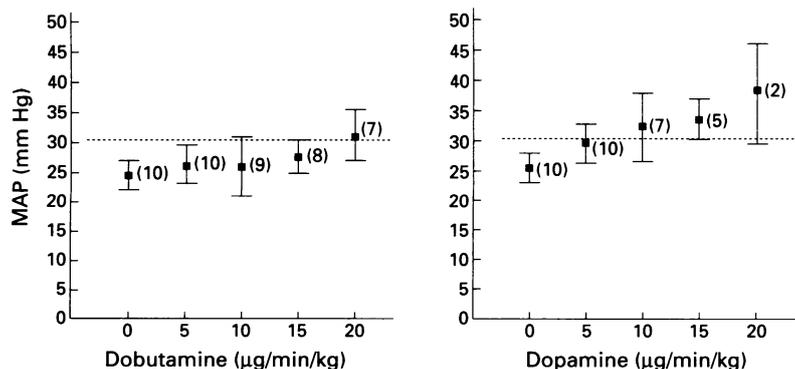 described in the literature, differ from one study to the other. Though all report an increase in MAP with dopamine,[3][20–22] its action on heart output seems to be more variable. Two clinical studies that monitored cardiac output in human neonates reported an increase in cardiac output under dopamine treatment.[21][22] In the second study, however,
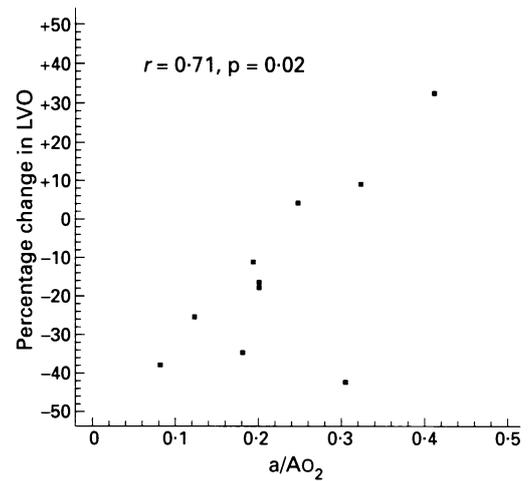

Figure 2 Relationship, in the dopamine group, between changes in LVO measured before dopamine administration and at the highest dopamine infusion rate, expressed in percent of the initial LVO, and the a/AO₂ on entry to trial. A significant negative correlation exists between a/AO₂ and the change in LVO.

r = 0·71, p = 0·02

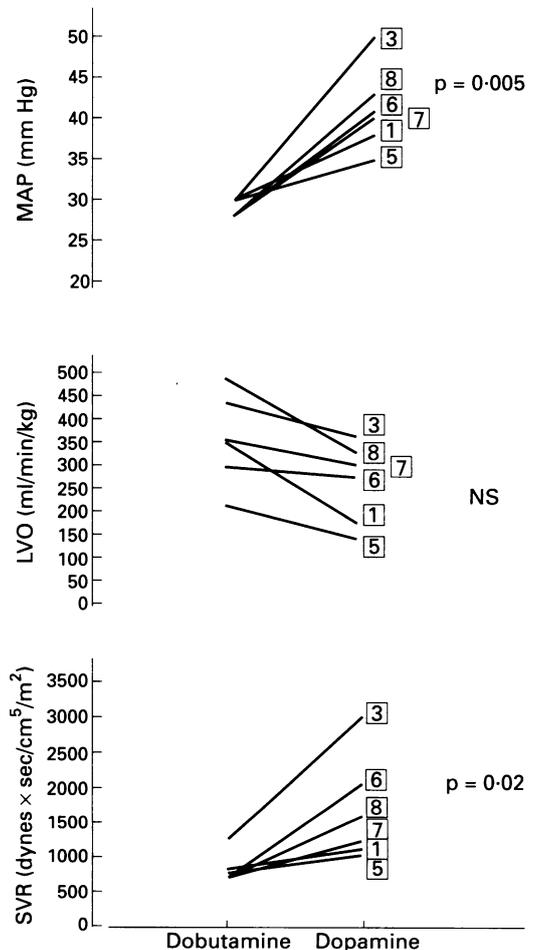p = 0·005

NS

p = 0·02

Dobutamine   Dopamine

Figure 3 Variation of MAP, LVO, and SVR during the switch from dobutamine at 20 μg/kg/min to dopamine at 20 μg/kg/min in the six infants in which dobutamine at 20 μg/kg/min failed to maintain MAP >30 mm Hg. Numbers inside the squares correspond to patient numbers in table 1.

Figure 1 Changes in MAP measured at 0, 5, 10, 15, and 20 μg/kg/min of dobutamine or dopamine in 20 hypotensive preterm infants. Means and 95% confidence intervals of the mean are indicated. The numbers in brackets indicate the number of babies receiving the dosage of the considered drug.

two types of responses were observed after dopamine infusion in six patients: in four cases where LVO was around 100 ml/min/kg before infusion, LVO was increased.[22] Conversely, in the two cases where initial LVO was high, in excess of 300 ml/min/kg, LVO was not or little modified after dopamine infusion. In our study, LVO was high, averaging 245 (23) ml/min/kg in the dopamine group. Conversely, in the study of Walther *et al* where LVO increased by 76% under dopamine, initial LVO was as low as 114 (26) ml/min/kg.[21] Besides the level of initial LVO, the severity of respiratory distress should also be taken into account. During hypoxia in newborn lambs, it was found that LVO increased only slightly under dopamine, then fell sharply at the highest dopamine doses.[7] In our study, a fall in LVO on dopamine was observed in seven infants; their mean a/AO$_2$ was 0·18 (0·02) but in the three infants where LVO had increased on dopamine it was 0·32 (0·05) (p=0·03). Moreover, we observed a significant relation between LVO modification on dopamine and a/AO$_2$. The drop in LVO was secondary to a rise in SVR that increased after the maximum dose. This effect in neonates has been attributed to dopamine stimulation of α adrenergic receptors[7 23] due to early maturation of these receptors.[5] Moreover, hypoxia is known to reduce the density of β adrenergic receptors.[24] This alpha predominant action may also induce pulmonary arterial hypertension[8 9] which, as in our case 13, can further enhance hypoxia.

Little is known about the effects of dobutamine during the neonatal period.[5] In adults dobutamine improves heart output, reduces SVR, but affects MAP very little, if at all, in terminal heart failure[25] or intensive surgery,[12] except in reducing hypotension during hypovolaemia. Only a few paediatric studies of the haemodynamic effects of dobutamine have been carried out.[10 11 26 27] Perkin *et al* reported that the effect of dobutamine on cardiac output was lower in infants under 12 months of age than in older children, whereas MAP was not significantly modified in either group.[11] Conversely, Stopfkuchen *et al* noted a significant increase in MAP in 12 of 14 cases of preterm infants born at 29 to 36 weeks' gestation, and demonstrated a significant inotropic effect by measurement of systolic time intervals.[10] In our study MAP increased significantly but insufficiently on dobutamine, lower than with dopamine, remaining below 31 mm Hg in six of 10 cases, despite a 21% increase in cardiac output. The increase in cardiac output can be attributed to the direct inotropic effect of the drug,[10] which is probably limited in the perinatal period.[28]

The initial aim of our study was to increase MAP above 30 mm Hg in order to prevent cerebral ischaemic lesions.[1 2] The essential question is whether it is better to increase MAP, even if LVO is reduced, or to tolerate lower MAP with higher output. The relation between cerebral flow and MAP, but not between cerebral flow and LVO, has been investigated in autoregulation studies in animal[29] and human[30] neonates. Studies of the relation between systemic haemodynamics and cerebral ischaemic lesions in very preterm neonates[1 2] have also relied on MAP and not on cardiac output as an indicator of systemic haemodynamics. It is difficult to provide a clear answer to our question as there are few data on the brain flow/LVO relationship. Mean cerebral velocity is apparently more dependent on MAP then on LVO.[31] Thus, there would seem to be a pressure threshold below which there is an increased risk of cerebral ischaemic lesions.

In summary, dopamine would thus seem more suitable than dobutamine as a means of increasing MAP in very preterm neonates. However, dopamine requires special care during hypoxia as there is a significant risk of LVO decrease due to the alpha vasoconstrictor effect. Dobutamine has the advantage of increasing LVO, but has a lesser effect on MAP. Non-invasive LVO monitoring can facilitate the choice of the best inotropic treatment in these hypotensive very preterm neonates.

1 Miall-Allen VM, De Vries LS, Whitelaw AGL. Mean arterial blood pressure and neonatal cerebral lesions. *Arch Dis Child* 1987; **62:** 1068–9.
2 Miall-Allen VM, de Vries LS, Dubowitz LMS. Blood pressure fluctuation and intraventricular hemorrhage in the preterm infant less than 31 weeks of gestation. *Pediatrics* 1989; **83:** 657–61.
3 Miall-Allen VM, Whitelaw AG. Response to dopamine and dobutamine in the preterm infant less than 30 weeks gestation. *Crit Care Med* 1989; **17:** 1166–9.
4 Zaristsky A, Chernow B. Use of catecholamines in pediatrics. *J Pediatr* 1984; **105:** 341–50.
5 Keeley SR, Bohn DJ. The use of intropic and afterload-reducing agents in neonates. *Clin Perinatol* 1988; **15:** 467–89.
6 Kligman R, Fanaroff AA. Caution in the use of dopamine in the neonate (letter). *J Pediatr* 1978; **93:** 540–1.
7 O'Laughlin MP, Fisher DJ, Dreyer QJ, Smith O. Augmentation of cardiac output with intravenous catecholamines in unanesthetized hypoxemic newborn lambs. *Pediatr Res* 1987; **22:** 667–74.
8 Mentzer RM, Alegre CA, Nolan SP. The effects of dopamine and isoproterenol on the pulmonary circulation. *J Thorac Cardiovasc Surg* 1976; **71:** 807–14.
9 Lang P, Williams RG, Norwood WI, Castaneda AR. The hemodynamic effects of dopamine in infants after corrective cardiac surgery. *J Pediatr* 1980; **96:** 630–4.
10 Stopfkuchen H, Queisser A, Vogel K. Cardiovascular responses to dobutamine determined by systolic time intervals in preterm infants. *Crit Care Med* 1990; **18:** 722–4.
11 Perkin RM, Levin DL, Webb R, Aquino A, Reedy J. Dobutamine: a hemodynamic evaluation in children with shock. *J Pediatr* 1982; **100:** 977–83.
12 Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport effects of dobutamine in critically ill general surgical patients. *Crit Care Med* 1986; **14:** 1033–7.
13 Anonymous. The arterial/alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis* 1974; **109:** 142–3.
14 Versmold HT, Kitterman JA, Phibbs RH, Gregory GA, Tooley WH. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4220 grams. *Pediatrics* 1981; **67:** 607–13.
15 Sonesson SE, Broberger V. Arterial blood pressure in the very low birth weight neonate. *Acta Paediatr Scand* 1987; **76:** 338–41.
16 Alverson DC, Eldridge MW, Dillon T, Yabek SM, Berman W. Non invasive pulsed Doppler determination of cardiac output in neonates and children. *J Pediatr* 1982; **101:** 46–50.
17 Windberg P, Janson M, Marions L, Lundell BPW. Left ventricular output during postnatal circulatory adaptation in healthy infants born at full term. *Arch Dis Child* 1989; **64:** 1374–8.
18 Snider AR. Two-dimensional and Doppler echocardiographic evaluation of heart disease in the neonate and fetus. *Clin Perinatol* 1988; **15:** 523–65.
19 Winberg P, Lundell PW. Left ventricular stroke volume and output in healthy term infants. *Am J Perinatol* 1990; **7:** 223–6.

20 Dissessa TG, Leitner M, Ti CC. The cardiovascular effects of dopamine in the severely asphyxiated neonate. *J Pediatr* 1981; **99:** 772–6.

21 Walther FJ, Bijan Siassi PD, Ramadan NA, Wu PYK. Cardiac output in newborn infants with transient myocardial dysfunction. *J Pediatr* 1985; **107:** 781–5.

22 Padbury JF, Agata Y, Baylen B, *et al.* Dopamine pharmacokinetics in critically ill newborn infants. *J Pediatr* 1987; **110:** 293–8.

23 Driscoll DJ, Gillette PC, Lewis RM, Hartley CJ, Schwartz A. Comparative hemodynamic effects of isoproterenol, dopamine and dobutamine in the newborn dog. *Pediatr Res* 1979; **13:** 1006–9.

24 Voelkel NF, Hegstrand L, Reeves JT, McMurty IF, Molinoff PB. Effects of hypoxia on density of beta-adrenergic receptors. *J Appl Physiol* 1981; **50:** 363–7.

25 Miller LW, Merkle EJ, Herrmann B. Outpatient dobutamine for end-stage congestive heart failure. *Crit Care Med* 1990; **18:** S30–3.

26 Schranz D, Stopfuchen H, Jungst BK. Haemodynamic

27 Stopfkuchen H, Schranz D, Huth R. Effects of dobutamine on left ventricular performance in newborns as determined by systolic time intervals. *Eur J Pediatr* 1987; **146:** 135–8.

28 Driscoll DJ, Gillette PC, Ezrailson EG, Schartz A. Inotropic response of the neonatal canine myocardium to dopamine. *Pediatr Res* 1978; **12:** 42–5.

29 Arnold B, Martin CG, Alexander BJ, Chen T, Fleming LR. Autoregulation of brain blood flow during hypotension and hypertension in infant lambs. *Pediatr Res* 1991; **29:** 110–5.

30 Lou HC, Lassen NA, Friis-Hansen B. Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 1979; **94:** 118–21.

31 Connors G, Hunse C, Gagnon R, Richardson B, Han V, Rosenberg H. Perinatal assessment of cerebral flow velocity wave forms in the human fetus and neonate. *Pediatr Res* 1992; **31:** 649–52.