A placebo-controlled study of the effects of dopexamine on gastric mucosal perfusion in infants undergoing hypothermic cardiopulmonary bypass

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We used a laser Doppler probe to measure gastric mucosal blood flow (flux) and a paediatric tonometer to intermittently calculate gastric–arterial P\textsubscript{CO\textsubscript{2}} difference (\textit{Pr}_\textsubscript{CO\textsubscript{2}}–\textit{Pa}_\textsubscript{CO\textsubscript{2}} gap) in 50 infants aged 0.3–52 weeks who required hypothermic cardiopulmonary bypass (CPB). During CPB, patients in group 2 (n=25) were given dopexamine 1.0 mg kg\textsuperscript{-1} over 5 min, followed by an infusion of 2 µg kg\textsuperscript{-1} min\textsuperscript{-1}. Patients in group 1 (n=25) received an equal volume of saline. Drug allocation was random and blinded. Measurements of flux, \textit{Pr}_\textsubscript{CO\textsubscript{2}}–\textit{Pa}_\textsubscript{CO\textsubscript{2}} gap and mean femoral arterial pressure (MAP) were made over 5 min during steady state before and after cooling on CPB to 18–24°C. MAP and blood lactate concentrations were similar in both groups throughout CPB. Mean flux decreased from 182 (SD 60) at the beginning of CPB to 158 (51) after rewarming on CPB in group 1, whereas it increased from 180 (56) to 196 (49) in group 2. This post-rewarm flux was significantly greater in group 2 than in group 1 (\textit{P}= 0.01). Similarly, mean \textit{Pr}_\textsubscript{CO\textsubscript{2}}–\textit{Pa}_\textsubscript{CO\textsubscript{2}} gap increased significantly from 3.6 (6.3) to 8.2 (6.7) in group 1 (\textit{P}=0.01) compared with a significant decrease from 5.8 (5.5) to 2.1 (5.5) in group 2 (\textit{P}=0.02). Mean \textit{Pr}_\textsubscript{CO\textsubscript{2}}–\textit{Pa}_\textsubscript{CO\textsubscript{2}} gap after rewarming in group 2 was significantly higher than that in group 1 (\textit{P}=0.001). These data indicate that dopexamine may be useful in maintaining normal gut perfusion in infants requiring hypothermic CPB.

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Our previous studies showed that transient gut mucosal ischaemia may occur in infants during and after cardiopulmonary bypass (CPB).\textsuperscript{1,3} Severe decreases in mucosal perfusion may be a causative factor in postoperative necrotizing enterocolitis\textsuperscript{4–6} and multiple organ dysfunction (MOF).\textsuperscript{7,8} In previous studies, we demonstrated that neonates with aortic arch anomalies\textsuperscript{2} and infants subjected to CPB-induced profound hypothermia\textsuperscript{1} may be at particular risk of developing splanchnic ischaemia in the perioperative period. CPB, even at a flow rate equivalent to a normal cardiac output, can reduce delivery of oxygen to the tissues by haemodilution,\textsuperscript{9,10} microvessel occlusion secondary to platelet or erythrocyte aggregation,\textsuperscript{11} and high blood concentrations of vasoconstrictor hormones such as angiotensin II,\textsuperscript{12} vasopressin,\textsuperscript{13} thromboxane,\textsuperscript{14} endothelin-1\textsuperscript{15} and catecholamines.\textsuperscript{16} Moreover, CPB flow rates are frequently reduced to a fraction of normal cardiac output, using profound hypothermia to reduce cellular oxygen requirements. Dopaminergic receptors have been identified in human intestinal villus and mucosal arterioles\textsuperscript{17} and increases in gastric mucosal blood flow, as measured using laser Doppler flowmetry (LDF), follow injection of dopamine into the gastric submucosa.\textsuperscript{18} A study in adults undergoing CPB showed that dopamine may increase gastric mucosal blood flow, as measured using LDF, by more than 85%.\textsuperscript{19} In contrast, however, adult patients with sepsis had a 28% decrease in mucosal blood flow after dopamine.\textsuperscript{20} Similarly, animal work suggests that low-dose dopamine may exacerbate gut ischaemia\textsuperscript{21} or reduce mucosal blood flow, despite increasing superior mesenteric arterial flow.\textsuperscript{22} Dopexamine has shown more consistent promise as a splanchnic vasodilator in experimental\textsuperscript{23–25} and clinical studies.\textsuperscript{26,27} In dogs, dopexamine is less potent than dopamine at dopaminergic (DA\textsubscript{1} and DA\textsubscript{2}) receptors but is a much more potent β\textsubscript{2}-adrenergic receptor agonist.\textsuperscript{28} Although agonist activity at either of these receptor subtypes decreases mesenteric arterial vascular resistance, β\textsubscript{2}-adrenergic receptor stimula-
tion may be more effective. However, although some clinical studies in critically ill adults that compared the effects of dopamine and dopexamine on gut mucosal perfusion showed dopexamine to be superior, other studies showed no significant difference between the two drugs. Moreover, it is probable that dopaminergic receptors undergo variable postnatal maturation, making extrapolation of data from adults to infants somewhat questionable.

There have been very few paediatric studies of the haemodynamic effects of dopexamine. One short-term clinical study in children with sepsis suggested that dopexamine 0.5–1\( \mu \)g kg\(^{-1}\) min\(^{-1}\) significantly improved splanchnic perfusion. However, a study in preterm neonates confirmed that dopexamine 2\( \mu \)g kg\(^{-1}\) min\(^{-1}\) increased global perfusion and arterial pressure and hence any beneficial effects that dopexamine may have on regional vascular perfusion may be secondary to an increase in cardiac output. Even in more sophisticated adult studies it has been difficult to differentiate the specific regional vascular effects of dopexamine from its direct and indirect effects on cardiac output.

CPB offers a useful physiological model to help clarify whether or not dopexamine can affect regional perfusion while cardiac output is kept constant. We demonstrated previously in an unblinded pilot study that dopexamine increased mucosal perfusion in infants undergoing CPB, and hence we wished to confirm these preliminary findings in a blinded, randomized, controlled study.

### Patients and methods

With Local Ethics Committee approval and written informed parental consent, we studied 50 infants, >3.0 kg in weight, aged 0.3–52 weeks, requiring >60 min elective hypothermic CPB. Patients requiring inotropic drugs before operation and those with aortic arch anomalies were excluded.

No premedication was given. Anaesthesia was induced with thiopental 4 mg kg\(^{-1}\) and neuromuscular block was achieved with vecuronium 0.2 mg kg\(^{-1}\) h\(^{-1}\). Anaesthesia was maintained with 5% isoflurane in oxygen and/or air before and after CPB, supplemented with alfentanil 10\( \mu \)g kg\(^{-1}\) i.v. followed by an infusion of 2\( \mu \)g kg\(^{-1}\) min\(^{-1}\). Midazolam 0.2 mg kg\(^{-1}\) was added to the pump prime blood. Routine monitoring included insertion of a cannula into the femoral artery for measurement of systemic arterial pressure. A paediatric TRIP tonometry catheter 8F (Datex-Ohmeda Ltd) was inserted via the mouth into the patient’s stomach and connected to a Tonocap monitor (Datex-Ohmeda Ltd) which intermittently analysed \( P_{\text{aco}_2} \) in the tonometer balloon (\( P_{\text{co}_2} \)). The monitor was calibrated previously in accordance with the manufacturer’s recommendations using a special gas mixture containing 5% carbon dioxide. Each measurement of \( P_{\text{aco}_2} \) was combined with a measurement of \( P_{\text{aco}_2} \) temperature corrected, to allow calculation of the \( P_{\text{aco}_2} \) gap.

Correct positioning of the tonometer was aided by the sight of a small bulging of the anterior abdominal wall as the catheter was advanced gently. In addition, after routine probe calibration, a laser Doppler probe (Moor Instruments Ltd) was slid into the lumen of a size 8-FG nasogastric tube and inserted into the stomach using the same technique as for the tonometry catheter. Positioning of the probe against the stomach wall was confirmed when the probe was connected to the MBF3 monitor (Moor Instruments Ltd) and computer by observing typical pulse synchronous oscillation. Later analysis of recordings was made using Moorsoft data interpretation software (Moor Instruments Ltd).

After sternotomy, but before surgical manipulation of the great vessels, baseline recordings of gastric mucosal flux, \( P_{\text{aco}_2} \), and femoral mean arterial pressure (MAP) were made over a 5-min period (pre-CBP). A sample of arterial blood was obtained for measurement of blood-gas values and blood lactate concentrations. The hollow fibre D701 oxygenator (Dideco) used for CPB was primed with warmed blood and crystalloid such that blood and core temperatures after initiation of CPB were approximately 34 ± 0.5°C and packed cell volume (PCV) was 25–30%. When the patient had been started on non-pulsatile CPB at a flow rate of 100 ml kg\(^{-1}\) min\(^{-1}\) for 10 min and nasopharyngeal temperature remained constant to within ±0.1°C, MAP, \( P_{\text{aco}_2} \), and oximetry values were recorded for another 5 min (W1.CPB). Another arterial blood sample was obtained for measurement of PCV, blood-gas values and lactate concentrations.

Patients were allocated randomly to one of two groups to receive either 0.9% saline (group 1) or dopexamine diluted in 0.9% saline (group 2), using a random figure table and sealed envelope system. An assistant, not otherwise involved in the study, prepared the drug syringes so that binding of the observer was maintained. Immediately after the first set of readings during CPB had been obtained, patients in group 2 received dopexamine 1.0 mg kg\(^{-1}\) over 5 min, followed by an infusion of 2\( \mu \)g kg\(^{-1}\) min\(^{-1}\). The control group received an equivalent infusion of saline. All infusions were given into a central vein. Patients were perfusion-cooled to 18–24°C, depending on the anticipated duration of low flow required. The rate of cooling and rewarming was controlled to approximately 1°C min\(^{-1}\). PCV was maintained at 25–30% throughout CPB by addition of blood or colloid as necessary. We ensured that mixed venous saturation was maintained >70% and \( P_{\text{aco}_2} \), kept at 10–20 kPa (depending on the pre-CBP \( P_{\text{aco}_2} \)) using inline electrodes (Polystan UK, Ltd). A capnograph (Datex Ohmeda Ltd), attached to the gas outlet port of the oxygenator, helped maintain a constant \( P_{\text{aco}_2} \) (5.3 ± 0.5 kPa, temperature uncorrected). When the patient was rewarmed on CPB to 34°C, and nasopharyngeal temperature and MAP had not changed significantly over a 5-min period, another set of blood-gas values, MAP, oximetry, and \( P_{\text{aco}_2} \) readings were obtained over 5 min (W2.CPB). When these rewarm readings were complete, the dopexamine/saline infusion was stopped, the heart was allowed to eject and patients...
were given inotropic support as required to aid weaning from CPB.

Our previous studies indicated that it is during rewarming that mucosal hypoxia is most likely to occur, and as ‘flux’ is an arbitrary unit of measurement, the change in flux (Aflux) from the first CPB reading (W1.CPB) to that recorded after rewarming (W2.CPB) was used as our primary outcome measure. Data from our preliminary unblinded pilot study were used to calculate the number of patients required in the study. Using a sample size of 25 for each group, we calculated that the study would have a power of more than 90% to yield a statistically significant result. This computation assumed that the mean difference in Δflux between groups would be at least 40 and the common within-group SD would be 40. This effect was selected as the smallest effect that would be clinically significant and that could be reasonably anticipated. Study data have not been invalidated these assumptions. We confirmed that our flux and PrCO₂ data were normally distributed using normal probability plots (SPSS v.9.0, SPSS UK Ltd). We used a two-sample t test to compare intra-group perfusion data and a paired t test to compare intra-group perfusion data. Normally distributed data are presented as mean (SD) and non-parametric data, such as weight and CPB time, are presented as median (interquartile range).

Results
Patients in group 1 were slightly younger and had slightly shorter operations than those in group 2, although these differences were not statistically significant. Eight patients in group 1 and 10 in group 2 were cyanosed before CPB, either because of tetralogy of Fallot or transposition of the great arteries. Most other patients had atrioventricular septal defects. Our measurements obtained before and after initiation of CPB confirmed that the two groups were comparable in global indices of perfusion (MAP and blood lactate concentrations) and regional indices of perfusion (flux and PrCO₂–PaCO₂ gap) (Tables 1, 2).

MAP measured at the initial CPB study period (W1.CPB) was significantly lower than that measured after rewarming to 34°C (W2.CPB) in both groups (P=0.03). Lactate concentrations increased in both groups, although this was significant only for group 1 (P=0.01). However, there were significant differences between the two groups in flux and intramucosal pH (pHi) (Table 2). In group 1, mean mucosal flux at W1.CPB was 182 (60) which decreased to 158 (51) after rewarming (W2.CPB) (P=0.02). In contrast, mean mucosal flux increased slightly from 180 (56) at W1.CPB to 196 (49) at W2.CPB in group 2 (ns). The gastric PrCO₂–PaCO₂ gap increased from 3.6 (6.3) to 8.2 (6.7) in group 1 (P=0.01) whereas it decreased slightly in group 2 from 5.8 (5.5) at W1.CPB to 2.1 (5.5) at W2.CPB (ns).

Table 1 Patient details and measurements obtained before cardiopulmonary bypass (CPB). Normally distributed data are presented as mean (sd) and non-parametric data as median [interquartile range]. PrCO₂–PaCO₂ gap= difference between PrCO₂ of gas in tonometer balloon and PaCO₂. MAP=mean femoral arterial pressure. No significant differences between groups.

<table>
<thead>
<tr>
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<th>Group 1 (n=25)</th>
<th>Group 2 (n=25)</th>
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<tbody>
<tr>
<td>Age (weeks)</td>
<td>18.4 [13.3]</td>
<td>25.3 [17.4]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.7 [1.4]</td>
<td>5.4 [4.0]</td>
</tr>
<tr>
<td>No. of cyanotic patients (%)</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>106 [44]</td>
<td>118 [108]</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>47 [23]</td>
<td>54 [28]</td>
</tr>
<tr>
<td>Flux (arbitrary units)</td>
<td>254 [82]</td>
<td>242 [62]</td>
</tr>
<tr>
<td>(PrCO₂–PaCO₂) gap (mm Hg)</td>
<td>–0.9 [4.3]</td>
<td>0.7 [4.4]</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>50.3 [8.4]</td>
<td>48.4 [10.4]</td>
</tr>
<tr>
<td>Lactate concn (mmol litre⁻¹)</td>
<td>1.3 [0.3]</td>
<td>1.2 [0.4]</td>
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Table 2 Mean (sd) gastric mucosal flux, gastric PrCO₂–PaCO₂ gap, mean femoral arterial pressure (MAP) and blood lactate concentrations in the two groups of patients at steady state after initiation of cardiopulmonary bypass (W1.CPB) and at steady state after rewarming to 34°C on CPB (W2.CPB). Patients in group 2 received a loading dose of doxapamine 1 mg kg⁻¹ after the initial CPB readings had been obtained, followed by an infusion of 2 µg kg⁻¹ min⁻¹ throughout CPB. Patients in group 1 were given an equivalent volume of saline. *P=0.01, **P=0.001 between groups.

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<th></th>
<th>Group 1 (n=25)</th>
<th>Group 2 (n=25)</th>
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<tr>
<td>W1.CPB flux (arbitrary units)</td>
<td>182 (60)</td>
<td>180 (56)</td>
</tr>
<tr>
<td>W1.CPB (PrCO₂–PaCO₂) gap (mm Hg)</td>
<td>3.6 (6.3)</td>
<td>5.8 (5.5)</td>
</tr>
<tr>
<td>W1.CPB MAP (mm Hg)</td>
<td>36 (13)</td>
<td>34 (10)</td>
</tr>
<tr>
<td>W1.CPB lactate concn (mmol litre⁻¹)</td>
<td>3.9 (0.9)</td>
<td>3.8 (1.0)</td>
</tr>
<tr>
<td>W2.CPB flux (arbitrary units)</td>
<td>158 (51)</td>
<td>196 (49)**</td>
</tr>
<tr>
<td>W2.CPB (PrCO₂–PaCO₂) gap (mm Hg)</td>
<td>8.2 (6.7)</td>
<td>2.1 (5.5)**</td>
</tr>
<tr>
<td>W2.CPB MAP (mm Hg)</td>
<td>43 (8.1)</td>
<td>46 (5.2)</td>
</tr>
<tr>
<td>W2.CPB lactate concn (mmol litre⁻¹)</td>
<td>5.2 (2.6)</td>
<td>4.5 (2.0)</td>
</tr>
<tr>
<td>∆Flux (W1.CPB flux–W2.CPB flux)</td>
<td>24 (46)</td>
<td>–19 (37)**</td>
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Discussion
We have shown that doxapamine increased gastric mucosal perfusion in infants after rewarming from profound hypothermia, with a significant increase in flux and a decrease in PrCO₂–PaCO₂ gap that were not seen in the control group. We are unaware of any comparable studies of the effects of doxapamine on splanchnic perfusion in infants or children undergoing cardiac surgery. Clinical studies involving adults undergoing normothermic cardiopulmonary bypass were unable to demonstrate a significant effect of doxapamine on pH during surgery. However, hepatic venous saturation did not change in these patients, suggesting adequate splanchnic oxygenation despite the decrease in pH. We believe, therefore, that our study is more likely to demonstrate drug-induced changes in gastric mucosal perfusion than studies in adult patients subjected to constant flow at normothermia. Although determination...
of optimum drug dose during CPB is problematic, the method has the particular advantage of allowing measurement of drug-induced changes in regional perfusion, without permitting any confounding effects of drug-induced changes in cardiac output.

It is common practice in most cardiac centres to continually monitor mixed venous saturation, mean arterial pressure and $P_{aDO_2}$ during CPB, together with intermittent measurement of blood-gas values and blood lactate concentrations. However, although these variables may be a useful guide to the adequacy of global oxygen delivery, they cannot exclude inadequate regional perfusion.\textsuperscript{38} 39 Experimental and clinical studies suggest that if pH\textsubscript{t} decreases or the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap increases while global indices of perfusion remain normal, mucosal hypoxia is a likely cause.\textsuperscript{40–42} Theoretical\textsuperscript{43} and clinical\textsuperscript{44} evidence suggests that the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap may be a more specific and reliable index of gastric mucosal oxygenation than pH\textsubscript{t}. Nevertheless, measurement of the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap provides only an indirect assessment of the adequacy of gastric mucosal perfusion. When blood flow to the mucosa decreases, the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap remains small until oxygen delivery becomes barely adequate to maintain normal tissue aerobic metabolism. It is only when blood flow decreases further that the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap increases. Hence any direct relationship between the $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap and more direct measures of mucosal blood flow such as flux occur at relatively low levels of mucosal perfusion.\textsuperscript{40} Measurements of gastric mucosal flux represent a real-time measure of blood flow, but in a small volume of tissue. The method involves shining a weak laser light out of a special probe and measuring the Doppler frequency shift in the reflected light induced by moving red blood cells. The limitations and inherent assumptions required by both of these methods of assessing gut mucosal perfusion have been discussed previously.\textsuperscript{1, 3, 12} 45 We believe they are sufficiently robust to draw the conclusion that the prevention and treatment of gut mucosal hypoxia in infants undergoing CPB is not only worthwhile but achievable. The consistent and divergent direction of change in both flux and $Pr_{CO_2}$\textsubscript{a}–$Pa_{CO_2}$ gap induced by dopexamine contrasts strikingly with the changes seen in the control group, despite similar values for global perfusion indices in the two groups.

The dose of dopexamine in our study was the same as that used in one neonatal trial\textsuperscript{34} but was twice as high as that used in children with sepsis.\textsuperscript{33} We deliberately chose a relatively high dose. The CPB circuit priming volume increased the total volume of circulating blood by at least 200\% for all patients. We used a loading dose of dopexamine and a high rate infusion continuing for at least 45 min in all patients so that we could be confident that blood concentrations of dopexamine were high enough to produce a therapeutic effect. Moreover, as dopexamine has no $\alpha$-adrenergic agonist effects,\textsuperscript{28} use of a high-dose regimen during CPB ensures maximum dopaminergic and $\beta_2$-adrenergic receptor agonism, with little danger of unwanted vasoconstriction. Although dopexamine is a weak inhibitor of neuronal catecholamine uptake, experimental studies suggest that any potential for vasoconstriction as a result of an increased blood concentration of norepinephrine is far outweighed by a dose-dependent increase in $\beta_2$-adrenergic receptor agonism.\textsuperscript{28} Relatively stable MAP readings throughout CPB in the dopexamine group support this hypothesis. Dopexamine, at an infusion rate of 2 $\mu$g kg$^{-1}$ min$^{-1}$, inconsistently increases heart rate in adults.\textsuperscript{46} 47 but this chronotropic effect is less obvious in neonates.\textsuperscript{34} Similarly, although we observed that mean heart rate in group 2 was higher than that in group 1 during rewarming, this difference was not clinically or statistically significant.

Further studies to define the optimum dose, duration of infusion and potential for adverse events should be performed before more general use of dopexamine in the perioperative period can be recommended for this age group. Furthermore, most infants undergoing profound hypothermia under CPB do not suffer from postoperative problems that can be related to gut mucosal hypoxia in the perioperative period. Hence routine use of dopexamine during CPB is unjustified. However, our data suggest that infants with aortic arch anomalies, who are at particular risk of gut mucosal hypoxia, may benefit from administration of dopexamine during CPB. Study of this particular subgroup of patients may need a multicentre approach.

Acknowledgements

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