Adverse Effects of Dopamine on Systemic Hemodynamic Status and Oxygen Transport in Neonates After the Norwood Procedure

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OBJECTIVES
The purpose of this study was to evaluate the effects of dopamine on hemodynamic status and oxygen transport in neonates after the Norwood procedure.

BACKGROUND
Dopamine is widely used to augment cardiac performance and increase oxygen delivery (DO2) in patients after cardiopulmonary bypass (CPB). This might be at the expense of increased myocardial and systemic oxygen consumption (VO2), thus offsetting the improved DO2. This balance is particularly fragile in critically ill neonates.

METHODS
Systemic oxygen consumption was continuously measured with respiratory mass spectrometry in 13 sedated, paralyzed, and mechanically ventilated neonates for 72 h after the Norwood procedure. Arterial, superior vena caval, and pulmonary venous blood gases were measured to calculate pulmonary blood flow (Qp), systemic blood flow (Qs), DO2, and oxygen extraction ratio (ERO2). Rate-pressure product was calculated. Dopamine at a dose of 5 μg/kg/min was routinely administered at cessation of CPB and terminated within the first 48 h. Hemodynamic and oxygen transport measures were obtained before and at 100 min after the termination of dopamine.

RESULTS
Terminating dopamine was not associated with significant changes in arterial pressure, Qp, Qs, or DO2 but was associated with a significant decrease in heart rate (p < 0.003), rate-pressure product (p = 0.03), and VO2 (−20 ± 11%, p < 0.0001), resulting in a significant decrease in ERO2 (p = 0.01).

CONCLUSIONS
Dopamine induces a significant increase in VO2 in neonates after the Norwood procedure, and termination is associated with an improved balance of VO2–DO2. These data further emphasize the importance of understanding changes in VO2 as well as DO2 in infants after cardiac surgery. (J Am Coll Cardiol 2006;48:1859–64) © 2006 by the American College of Cardiology Foundation

Dopamine, a precursor in the endogenous synthesis of norepinephrine, is widely used to augment cardiac performance and increase oxygen delivery (DO2) to tissues in critically ill patients with low cardiac output state (1–3), including those after cardiopulmonary bypass surgery (CPB) (4–7). It is well known that catecholamines might increase myocardial oxygen consumption; however, they might also increase systemic oxygen consumption (VO2). This occurs in 2 ways: first, by kindling cell metabolism via adrenergic receptors; and second, by their action on the central nervous system and endogenous sympathetic drive (8–12). Nonetheless, if the increase in DO2 is greater relative to VO2, dopamine might improve the overall balance of oxygen transport and tissue oxygenation, and some have reported favorable responses to dopamine treatment in adults and older children after cardiac surgery (4–7). In neonates, however, unlike in the adult or older child, little or no information is available about the effects of dopamine on VO2–DO2 relationship. This is of particular relevance in neonates undergoing CPB to repair complex congenital heart defects, such as the Norwood procedure, because of their limited myocardial functional reserve and the significantly elevated VO2 secondary to the systemic inflammatory response to CPB (13). Furthermore, neonates have abundant brown adipose tissue that is richly populated by β-adrenergic receptors, via which catecholamines can stimulate thermogenesis and a substantial increase in VO2 (14). Indeed, experimentally, dobutamine increased body temperature, VO2, and oxygen extraction ratio (ERO2) in neonatal lambs, an effect abrogated by adrenergic blockade (15). The relevance of this study to neonates undergoing cardiac surgery is less clear, however. Dobutamine is used relatively rarely in this population, and the adverse effect on ERO2 was only observed at relatively high doses. Furthermore, although the effects on thermogenesis and body temperature were important observations, body temperature is tightly controlled in postoperative children, because of its known relationship with VO2 (16,17). Thus, in the present study we examined the effect of dopamine on the balance between VO2 and DO2 in eutermic neonates during the early postoperative period after the Norwood procedure.
Modified ultrafiltration was performed in all patients. A pulmonary venous line was inserted into the orifice of the right upper pulmonary vein. A direct oximetric sampling catheter was inserted in the superior vena cava.

**Postoperative management.** Our protocol for management was as follows: the central temperature (esophageal) was maintained between 36° and 37°C. Postoperative monitoring included arterial, superior vena cava, and pulmonary venous pressures; heart rate; and end-tidal carbon dioxide. Sedation consisted of continuous intravenous infusion of morphine and intermittent injections of a muscle relaxant (pancuronium) and lorazepam as required. Patients received time cycled pressure control/pressure support ventilation. Ventilation volume and rate were adjusted to control partial pressure of arterial carbon dioxide. Arterial oxygen saturation was maintained between 70% and 85%. Hemoglobin was maintained between 14 and 16 mg/dl. Vasoactive drugs (milrinone, phenoxybenzamine, and vasopressin) and volume infusions (5% albumin or blood) were administered according to our standard protocol (19). Dopamine was subsequently discontinued when the hemodynamic status and ventricular function were deemed satisfactory and restarted according to clinical judgment.

**Methods of measurements. PATIENT MONITORING.** All patients had continuous invasive monitoring of systemic, superior vena cava, and pulmonary venous pressures. Heart rate was continuously monitored, as was the central body temperature (esophageal).

**OXYGEN CONSUMPTION.** Systemic oxygen consumption was measured continuously with an AMIS2000 mass spectrometer (Innovision A/S, Odense, Denmark). This is a sensitive and accurate method for continuous gas analysis that allows simultaneous measurements of multiple gas fractions (20).

**CALCULATIONS OF HEMODYNAMIC STATUS AND OXYGEN TRANSPORT.** Blood samples were taken from the arterial, superior vena cava, and pulmonary vein lines for the

**Table 1. Clinical Data for the 13 Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Days)</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>CPB (Min)</th>
<th>ACC (Min)</th>
<th>Circulatory Arrest (Min)</th>
<th>Cerebral Perfusion (Min)</th>
<th>Diagnosis</th>
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<tr>
<td>1</td>
<td>9</td>
<td>3.6</td>
<td>0.24</td>
<td>109</td>
<td>50</td>
<td>4</td>
<td>44</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3.5</td>
<td>0.23</td>
<td>108</td>
<td>47</td>
<td>12</td>
<td>35</td>
<td>HLHS, AS, MS</td>
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<tr>
<td>3</td>
<td>4</td>
<td>3.7</td>
<td>0.25</td>
<td>151</td>
<td>100</td>
<td>35</td>
<td>53</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>4.2</td>
<td>0.27</td>
<td>122</td>
<td>62</td>
<td>3</td>
<td>60</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>3.5</td>
<td>0.23</td>
<td>165</td>
<td>75</td>
<td>13</td>
<td>59</td>
<td>DILV, TGA</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>3.5</td>
<td>0.23</td>
<td>172</td>
<td>82</td>
<td>9</td>
<td>70</td>
<td>HLHS, AA, MA</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>3.9</td>
<td>0.25</td>
<td>170</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>4</td>
<td>0.25</td>
<td>167</td>
<td>64</td>
<td>17</td>
<td>44</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>2.9</td>
<td>0.2</td>
<td>142</td>
<td>62</td>
<td>1</td>
<td>62</td>
<td>HLHS, AS, MS</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>4.5</td>
<td>0.28</td>
<td>103</td>
<td>75</td>
<td>45</td>
<td>30</td>
<td>DILV, TGA</td>
</tr>
<tr>
<td>11</td>
<td>7</td>
<td>2.8</td>
<td>0.19</td>
<td>66</td>
<td>59</td>
<td>17</td>
<td>20</td>
<td>HLHS, AA, MA</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
<td>3.6</td>
<td>0.24</td>
<td>156</td>
<td>86</td>
<td>0</td>
<td>0</td>
<td>Criss-cross heart, VSDs</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>4.2</td>
<td>0.27</td>
<td>127</td>
<td>99</td>
<td>44</td>
<td>49</td>
<td>HLHS, AA, MA, TAPVC</td>
</tr>
</tbody>
</table>

AA = aortic atresia; ACC = aortic cross clamp; AS = aortic stenosis; CPB = cardiopulmonary bypass; DILV = double inlet left ventricle; DORV = double outlet right ventricle; HLHS = hypoplastic left heart syndrome; LV = left ventricle; MA = mitral atresia; MS = mitral stenosis; TAPVC = total abnormal pulmonary venous connection; TGA = transposition of great arteries; VSDs = multiple ventricular septal defects.
Dopamine was administered at the cessation of CPB at 5 µg/kg/min in 12 patients and 7.5 µg/kg/min in the remaining 1 (Patient 4) and subsequently terminated within the first 48 h in all patients. Table 3 and Figure 1 show the changes in systemic hemodynamic condition and oxygen transport at termination of dopamine. During the study period, temperature was unchanged (p > 0.05). Termination of dopamine of 5 µg/kg/min (7.5 µg/kg/min in Patient 4) was associated with a significant reduction in heart rate by a mean of 12 ± 12 beats/min (p = 0.003) but not with arterial blood pressure (p > 0.05), resulting in a significant decrease in rate–pressure product (p = 0.03). There were no significant changes in PVR-BT and Qp, SVR and Qs, Qp/Qs, CO, stroke volume, and DO2 (p > 0.05 for all). The VO2 uniformly decreased in all patients from 105 ± 23 ml/min/m² to 84 ± 23 ml/min/m² (p < 0.0001), representing a 20 ± 11% decrease. Figure 2 shows the examples of on-line measurement of VO2 around the time of terminating dopamine in 3 individual patients representing a small (A, Patient 3), moderate (B, Patient 2), and great (C, Patient 4) reduction of VO2. The drop in VO2 is clearly demonstrated immediately after the termination of dopamine. In the patient (Patient 4) who was given dopamine of 7.5 µg/kg/min, VO2 decreased by 39% (from 84 to 50 ml/min/m²), the greatest among the patients (Fig. 2C). The decrease in VO2 resulted in a significant decrease in ERO2 from 0.35 ± 0.10 to 0.28 ± 0.08 (p = 0.01). There was no correlation between the age, body weight, or body surface area and the decrease in VO2 (R² = 0.10 to 0.14, p > 0.05 for all). Arterial lactate also decreased significantly (p = 0.05).

**DISCUSSION**

This study shows that in neonates after the Norwood procedure, dopamine has adverse effects on the balance of VO2 and DO2. Early termination of dopamine was associated with a significant decrease in VO2 leading to an improved VO2–DO2 balance reflected by a significant decrease in ERO2. It is likely that these counterintuitive effects of dopamine largely reflect the stimulation of non-cardiac tissue metabolism.

Dopamine was first synthesized one century ago (22) and has been widely used for 40 years (1–7) to augment cardiac performance in different forms of low cardiac output state. Dopamine has differential agonist effects on the 3 main systems: measurements of blood gases and oxygen saturation. Pulmonary blood flow (Qp) and systemic blood flow (Qs) were then calculated with the direct Fick method. Total cardiac output (CO), DO2, systemic vascular resistance (SVR), pulmonary vascular resistance inclusive of the Blalock-Taussig shunt (BT-PVR), and ERO2 were calculated with standard equations. Stroke volume was calculated as cardiac output divided by heart rate. The rate–pressure product was calculated by multiplying the heart rate by the systolic arterial blood pressure, an indirect index of myocardial VO2 (21) (Table 2).

**Table 2. Equations Using Oxygen Consumption (VO2) to Calculate Hemodynamics and Oxygen Transport Parameters**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qp (l/min/m²)</td>
<td>VO2/(CaO2 – Cvo2)</td>
</tr>
<tr>
<td>Qs (l/min/m²)</td>
<td>VO2/(CpvO2 – Cvo2)</td>
</tr>
<tr>
<td>CO (l/min/m²)</td>
<td>Qp + Qs</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>CO/heart rate × 1,000</td>
</tr>
<tr>
<td>SVR (Wood unit × m²)</td>
<td>(MAP – MPVP)/Qp</td>
</tr>
<tr>
<td>BT-PVR (Wood unit × m²)</td>
<td>(MAP – MPVP)/Qp</td>
</tr>
<tr>
<td>DO2 (ml/min/m²)</td>
<td>Qp × CaO2</td>
</tr>
<tr>
<td>ERO2</td>
<td>VO2/DO2</td>
</tr>
<tr>
<td>Rate-pressure product (unit)</td>
<td>Heart rate × SAP</td>
</tr>
</tbody>
</table>

**Study protocol.** Patients were studied during the first 72 h after arrival in the cardiac intensive care unit. Measurements of VO2 were recorded continuously. However, for the purpose of analysis, averaged recordings were made during a 30-min period just before and a 30-min period at 100 min after the termination of dopamine. Measurements of other systemic hemodynamic and oxygen transport were also obtained within the periods. Patients were excluded if any changes in other treatments were made during the study period.

**Data analysis.** Data are expressed as mean values ± SD. The data, collected before and after termination of dopamine, were analyzed by paired t test. A p value < 0.05 was considered statistically significant.

**RESULTS**

Dopamine was administered at the cessation of CPB at 5 µg/kg/min in 12 patients and 7.5 µg/kg/min in the remaining 1 (Patient 4) and subsequently terminated within the first 48 h in all patients. Table 3 and Figure 1 show the changes in systemic hemodynamic condition and oxygen transport at termination of dopamine. During the study period, temperature was unchanged (p > 0.05). Termination of dopamine of 5 µg/kg/min (7.5 µg/kg/min in Patient 4) was associated with a significant reduction in heart rate by a mean of 12 ± 12 beats/min (p = 0.003) but not with arterial blood pressure (p > 0.05), resulting in a significant decrease in rate–pressure product (p = 0.03). There were no significant changes in PVR-BT and Qp, SVR and Qs, Qp/Qs, CO, stroke volume, and DO2 (p > 0.05 for all). The VO2 uniformly decreased in all patients from 105 ± 23 ml/min/m² to 84 ± 23 ml/min/m² (p < 0.0001), representing a 20 ± 11% decrease. Figure 2 shows the examples of on-line measurement of VO2 around the time of terminating dopamine in 3 individual patients representing a small (A, Patient 3), moderate (B, Patient 2), and great (C, Patient 4) reduction of VO2. The drop in VO2 is clearly demonstrated immediately after the termination of dopamine. In the patient (Patient 4) who was given dopamine of 7.5 µg/kg/min, VO2 decreased by 39% (from 84 to 50 ml/min/m²), the greatest among the patients (Fig. 2C). The decrease in VO2 resulted in a significant decrease in ERO2 from 0.35 ± 0.10 to 0.28 ± 0.08 (p = 0.01). There was no correlation between the age, body weight, or body surface area and the decrease in VO2 (R² = 0.10 to 0.14, p > 0.05 for all). Arterial lactate also decreased significantly (p = 0.05).
types of adrenergic receptors that are dose dependent. At low doses (<3 \( \mu g/min/kg \)), the effect of stimulation of dopaminergic receptors predominates, inducing a direct arteriolar vasodilation to increase renal blood flow and an indirect increase in cardiac output. At moderate doses (>4 \( \mu g/min/kg \)), beta-adrenergic receptor stimulation (mainly \( \beta_1 \) and \( \beta_2 \)) produces inotropic effects to increase stroke volume and cardiac output. Higher doses (>8 \( \mu g/min/kg \)) are now rarely used because of vasoconstriction provoked by alpha-adrenergic receptor stimulation (23).

Although exerting inotropic effects, adrenergic receptor stimulation also increases metabolic rate, manifest as an increase in VO\(_2\). This phenomenon was described 75 years ago, in studies of epinephrine in normal adults (24). Subsequent studies in animals have shown that the effects of catecholamines on cellular metabolism and thermogenesis are mediated by \( \beta_1 \), \( \beta_2 \), and particularly \( \beta_3 \)-adrenergic receptor stimulation (9); might be potentiated by alpha-adrenergic receptor agonist (10,11); and might possibly involve dopaminergic receptor stimulation (12). All of these receptors are densely expressed in brown adipocytes located in brown adipose tissue. Brown adipose tissue is abundant in human neonates (14). Activation of brown adipocytes by catecholamines, particularly by norepinephrine, plays a crucial role in non-shivering thermogenesis, by means of stimulating fatty acid oxidation and uncoupling the respiratory chain from adenosine triphosphate (ATP) synthesis to produce a large amount of heat through uncoupling protein 1 (9,14). Experimentally, dopamine, as a precursor in the endogenous synthesis of norepinephrine, seems to have similar potency to norepinephrine in terms of increased metabolic and VO\(_2\) responses (25,26). Thus, both circulatory and metabolic stimulating effects by catecholamines share the same adrenergic signaling mechanisms. If the circulatory responses to adrenergic stimulation are reduced, or the metabolic responses enhanced, the beneficial effects of catecholamine stimulation might be abrogated.

Such is the case in patients, particularly neonates, after CPB. Systemic oxygen delivery is often low during the first 24 h, owing to myocardial injury resulting directly from surgery and indirectly from ischemia-reperfusion injury and the systemic inflammatory response (13,17,27). Furthermore, neonatal hearts are known to have limited reserve to increase cardiac contractility. The reserve might become marginal in a Norwood circulation with the injured single right ventricle providing parallel pulmonary and systemic circulations (13). In these patients, efforts to improve DO\(_2\) by catecholamines might be more likely to be associated with predominately adverse effects. This was the case in our studies. Dopamine exerted a primarily chronotropic rather than inotropic effect, as indicated by the significant decrease in heart rate (p = 0.003) but insignificant change in stroke volume (p > 0.05) after termination of dopamine. Overall, the use of dopamine did not increase DO\(_2\) and seemed to cause an increase in myocardial VO\(_2\), as indicated by the significantly higher rate-pressure product (p = 0.03).
Whereas DO₂ is depressed, VO₂ is increased during the early hours after CPB, owing mainly to systemic inflammatory response and repayment of oxygen debt accumulated from CPB (17,28), thus further burdening myocardial function. We have recently demonstrated that increased VO₂ is the major contributor to the impairment of oxygen transport in neonates during the first 24 h after the Norwood procedure (13), and any treatment that might further increase VO₂ is clearly undesirable. There is experimental evidence (15) that neonates might be particularly susceptible to the metabolic effects of catecholamines. Penny et al. (15) showed that dobutamine, a derivative of dopamine, increased DO₂ similarly in 3 age groups of lambs, but the increase in VO₂ was 7- to 12-fold greater in newborns (1 to 2 days) as compared with the older groups (7 to 10 days and 6 to 8 weeks, respectively) and at higher doses was associated with an increase in ERO₂. This study demonstrated a significant thermogenic effect of dobutamine, there being a significant rise in central temperature. In children after open heart surgery, central hyperthermia is associated with increased VO₂ (16). Indeed, we have previously shown an approximately 11% increase in VO₂ for every 1°C rise in temperature above 36°C (16). For this reason, euthermia should be vigorously maintained in postoperative children. This makes previous experimental observations regarding the thermogenic and calorigenic effects of catecholamines difficult to translate to clinical relevance. Nonetheless, in our human neonatal studies, termination of dopamine of 5 μg/min/kg was associated with a substantial decrease in VO₂ by approximately 20%. Consequently, given the insignificant change in DO₂, ERO₂ improved; while possibly a surrogate phenomenon, the concomitant fall in arterial lactate levels also suggests improved systemic metabolic efficiency.

**Study limitations.** We could only measure global VO₂ and therefore were unable to dissect the myocardial and systemic elements of the VO₂ responses. Furthermore, because different organs have different distribution of adrenergic receptor subtypes, regional VO₂–DO₂ mismatch might be non-uniform with dopamine treatment. Future studies should analyze the potential differential effects on the heart (29,30), splanchnic organs (31), and the brain (32). However, such an assessment of regional effects would likely require direct instrumentation of the target organ, which is impractical in a clinical study.

We were unable to examine a “dose response” effect of dopamine dosage, again because our protocol was constrained by clinical practice. Nonetheless, our predominant dose of 5 μg/kg/min reflects the commonest dose used in clinical practice, and adverse effects at this dose were clear. Finally, we are unable to comment on the effects of dopamine, beneficial or detrimental, when given at other times during postoperative course. However, it is reasonable to conclude that outside of the immediate 48 postoperative hours, the effects of dopamine might be adverse in this patient group. Indeed, it is now our practice to stop dopamine as early as possible after the return to the cardiac intensive care unit.

Finally, we studied a discrete anatomic subset of neonates undergoing the Norwood procedure. Although this avoids the confounding issues of multiple diseases and operative strategies, our data cannot be extrapolated to all neonates undergoing cardiac surgery. Nonetheless, it seems unlikely that the responses are entirely specific.

**Conclusions.** In neonates during the early postoperative period after the Norwood procedure, a moderate dose of dopamine induces a predominant increase in VO₂, adversely affecting the VO₂–DO₂ relationship. Termination of dopamine is associated with an improved VO₂–DO₂ balance and reduced lactate production. Thus, dopamine should be used with caution in neonates after CPB. These data further emphasize the importance of understanding changes in VO₂ as well as DO₂ in infants after cardiac surgery.

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REFERENCES