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## Dopamine

### *One Size Does Not Fit All*

THE use of positive inotropic agents to improve organ perfusion varies widely from institution to institution. However, the practice of infusing dopamine at doses at  $1-3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ("renal" dose) to improve renal function is fairly ubiquitous. The report by MacGregor *et al.*<sup>1</sup> in this month's *ANESTHESIOLOGY* addresses the pharmacokinetic issues underlying this practice. Their results, in conjunction with review of the pharmacodynamic properties of dopamine, provide insight into the ambiguous, and often disappointing, results of attempts to provide "protection" for patients at risk for renal injury.

The use of dopamine to modulate renal function dates from studies in the 1960s that show increased renal plasma flow, glomerular filtration rate (GFR), and diuresis and natriuresis in volunteers and in patients in congestive heart failure.<sup>2,3</sup> In most studies in which cardiac index was measured, the improvement in renal function was associated with increased cardiac index, and it has been difficult to distinguish effects on the renal vasculature from global hemodynamic effects. Selective dopamine-induced renal vasodilation has been observed in studies of animals and healthy human volunteers. In a rat model, administration of dopamine caused dilation of

renal efferent and afferent arterioles in low concentrations and vasoconstriction at higher concentrations, and  $\alpha$ -adrenergic blockade reversed the latter effect. Studies of healthy dogs and humans indicate that renal vasodilation in excess of systemic vasodilation occurs at some doses, although this was not observed in studies of septic animals. There has been no study to confirm selective renal vasodilation in patients at risk for renal injury. Also, dopamine-induced increases in GFR, independent of global hemodynamic effects, have not been shown consistently. Renal vasodilation could actually decrease GFR, depending on the balance of efferent and afferent dilation. The diuresis and natriuresis usually observed after dopamine administration cannot be attributed to increased GFR because increased urine volume and sodium excretion is seen when GFR does not change. Rather, diuresis and natriuresis is caused by inhibition of tubular sodium-potassium adenosine triphosphate (ATPase), an effect independent of either renal or global hemodynamic effects.

Although dopamine is widely used for renal protection, well-controlled trials of dopamine in patients at risk for renal dysfunction or after acute renal injury have not, in general, supported this practice. The tubular effects of dopamine or increased cardiac output may account for reports that show increased urine output and creatinine clearance with dopamine in surgical patients (cardiac surgery and liver transplantation). Certainly, numerous other studies of surgical patients have failed to show any beneficial renal effect of dopamine. Consideration of the basic pharmacology of dopamine may explain the conflicting results.<sup>4</sup> Dopamine is a relatively nonspecific agonist, with activity at both the dopamine-1 (DA-1) and dopamine-2 (DA-2) receptors and the  $\alpha$ - and  $\beta$ -adrener-

This Editorial View accompanies the following article: MacGregor DA, Smith TE, Prielipp RC, Butterworth JF, James RL, Scuderi PE: Pharmacokinetics of dopamine in healthy male subjects. *ANESTHESIOLOGY* 2000; 92:338-46

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gic receptors. DA-1 receptors are postsynaptic and, when activated, elicit vasodilation and inhibition of sodium-potassium adenosine triphosphate. DA-2 receptors are less well-understood. They are presynaptic and inhibit adenylate cyclase activity (in contrast to DA-1 receptors) and norepinephrine release. Blockade of DA-2 receptors has been shown to increase renal blood flow and GFR, indicating that DA-2 receptor activation decreases renal blood flow. Also  $\alpha$ -agonist activity will cause vasoconstriction, decreasing renal blood flow, as shown by the reversal of dopamine-induced renal vasoconstriction by the  $\alpha$  blockade noted previously.

The relative agonist activities of dopamine and, hence, the pharmacologic effects are concentration-dependent, and it is in this regard that the study by MacGregor *et al.*<sup>1</sup> is highly relevant. These investigators administered dopamine at doses of  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  and  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  to nine healthy volunteers. Arterial blood samples were taken for analysis of dopamine plasma concentration. The higher dose of dopamine was administered first for 10 min, followed by a 30-min washout phase, and then the lower dose was given for 90 min, followed by another 30-min washout. The data were analyzed using a standard two-compartment model. Their principal observation was a 10- to 75-fold variation in plasma concentrations during the infusion of dopamine and an even greater variability in baseline levels. Although pharmacokinetic parameters were derived, these are of less interest than the large variation in steady state plasma concentrations despite weight-based dosing in a homogeneous group of subjects.

Is there an explanation for these results other than very pronounced pharmacokinetic variability? Certainly, this large variability in plasma concentration could lead one to question the assay, but the assay used for this study is well-validated. Of greater concern is the experimental design. The sequence of dopamine doses was not randomized and the  $10\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion preceded the  $3\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion in each subject. The investigator's rationale for this design is understandable. The  $10\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion was limited to 10 min because of concern about unpleasant side effects in volunteers and the prolonged infusion ( $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) was given last because of concerns about drug accumulation and the need for a longer washout phase. Nevertheless, it is possible that the biologic effects of the higher dose could have influenced the kinetics at the lower dose. For example, a subject's anxiety during the  $10\text{-}\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dose may increase endogenous catecholamine levels and contribute to

higher levels during the subsequent infusion at  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . In this case, the large variability in plasma dopamine concentrations may reflect, not so much kinetic variability, as variability in the response to dopamine, a pharmacodynamic effect.

The authors use a standard two-compartment model with an absorption lag to describe the plasma concentrations as a function of time. As the authors note, this model may be a gross oversimplification because dopamine, by altering cardiac output, may influence its own pharmacokinetics. Such nonlinear kinetics could help account for the observed results because pharmacokinetic and pharmacodynamic variability both would then influence plasma concentrations.

The variability in dopamine concentrations could be caused by differences in drug distribution, elimination, nonlinear kinetics, or the endogenous levels (other investigators have demonstrated large variations in endogenous catecholamine concentrations). Regardless of why this variability exists, the study by MacGregor *et al.*<sup>1</sup> shows that a subject receiving "renal-dose" dopamine may have plasma levels higher than some other subject receiving  $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  dopamine. This observation has important implications for the use of dopamine for its renal effects. Given the variety of agonist activities of dopamine (DA-1, DA-2,  $\alpha$ ,  $\beta$  receptors) and the disparate effects of these receptors (renal vasodilation with DA-1 activity and renal vasoconstriction with  $\alpha$  and DA-2 activity), this variability in plasma concentrations implies that the renal effects cannot be predicted by the dose of dopamine. Renal-dose dopamine may induce renal vasodilation with increased renal blood flow in one patient and renal vasoconstriction with decreased renal blood flow in another. In principal, increasing renal blood flow should be more reliably achieved using a pure DA-1 agonist, such as fenoldopam. One could predict that plasma concentrations of fenoldopam would also be highly variable. However, the fact that it is a pure DA-1 agonist, without significant activity at DA-2,  $\alpha$ , or  $\beta$  receptors, makes it understandable why fenoldopam increases renal blood flow in a dose-dependent manner. Renal dopamine may be indicated when one desires a positive inotropic effect plus diuresis and natriuresis (*via* sodium-potassium adenosine triphosphate inhibition in the tubule). But increased renal blood flow is not guaranteed. The report by MacGregor *et al.*<sup>1</sup> makes us realize that the renal effects of dopamine are not predicted by the dose. Of course, anesthesiologists should have suspected this. We all know that anesthesia is not induced in all patients by 3.5 mg/kg sodium thiopental. It was unreal

istic to believe then that a single dose of dopamine would have the same renal effects in all patients.

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## Improving Splanchnic Perfusion during Cardiopulmonary Bypass

IMPAIRED perfusion and distribution of blood flow away from visceral organs during cardiopulmonary bypass (CPB) have been implicated as causing mucosal ischemia, intraluminal acidosis, altered gut permeability, and endotoxemia.<sup>1-8</sup> Although the overall incidence of gastrointestinal complications after cardiac operations is relatively low (0.6-2.0%), associated perioperative mortality can be significantly increased 15% to 63%.<sup>1-3</sup> Accordingly, maintaining or increasing splanchnic perfusion during CPB may be important in selected patients. In this issue of *ANESTHESIOLOGY*, Bastien *et al.*<sup>9</sup> use a rabbit CPB model to examine the relative importance of altering blood pressure or pump flow rate on splanchnic perfusion as measured by laser Doppler flowmetry (LDF) in the gastric, jejunal, ileal, and hepatic regions. The authors report that a high pump flow rate (100 ml · kg<sup>-1</sup> · min<sup>-1</sup>) improves intestinal mucosal perfusion significantly more than a low pump flow rate (50 ml · kg<sup>-1</sup> · min<sup>-1</sup>), whereas altering aortic pressure by infus-

ing vasodilator or vasoconstrictor drugs fails to increase mucosal blood flow. Over the range of 50-500 ml/min, increasing pump flow rate linearly increases gastric and ileal LDF values. The authors conclude that normothermic CPB reduces splanchnic perfusion and attenuates autoregulation so that a linear relationship exists between CPB flow rate and splanchnic LDF. Aortic blood pressure does correlate with LDF in ileal and gastric regions, although the variability of this relationship is so great that any benefit of increasing aortic pressure on intestinal LDF becomes less predictable.

This study does have several limitations, such as: (1) the use of an invasive animal preparation, where lower-extremity circulation is eliminated; (2) lack of confirmatory data using alternative techniques to quantitate blood flow, such as microspheres or electromagnetic flowmetry; (3) bolus drug administration as opposed to constant infusion; (4) an unblinded protocol without concurrent controls; and (5) lack of outcome measures such as animal survival, intraabdominal complications, and long-term effects of altered gut perfusion. Nevertheless, this study illustrates that a major determinant of splanchnic mucosal perfusion during CPB is pump flow rate—not aortic blood pressure—and that altering blood pressure with vasoactive drugs, whether at low or high pump flow rates, fails to improve intestinal LDF.

In reviewing the consequences of nonpulsatile CPB on intestinal perfusion, several important aspects become apparent:

This Editorial View accompanies the following article: Bastien O, Piriou V, Aouifi A, Flamens C, Evans R, Lehot JJ: Relative importance of flow *versus* pressure in splanchnic perfusion during cardiopulmonary bypass in rabbits. *ANESTHESIOLOGY* 2000; 92:457-64.

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