

COMMENTARY

# Dopexamine: immunomodulatory, hemodynamic, or both?

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See related research by Bangash *et al.*, <http://ccforum.com/content/17/2/R57>

## Abstract

Dopexamine is a dopamine analog that has been used for hemodynamic optimization in a number of clinical settings. This animal investigation showed anti-inflammatory effects of dopexamine in a rat endotoxin model without effects on global or regional flow, but it is not time to dispense with hemodynamics altogether just yet. Rather, an integrative approach to the effects of catecholamines, considering both inflammatory and hemodynamic effects, including those on the microcirculation, can help clinicians best understand how to employ them in clinical practice.

## Introduction

Busy clinicians sometimes think twice before reading studies of animal models. Yes, it sounds interesting, but is it really going to change my practice? There is so much else I should be reading... This writer does not mean to cast aspersions on such an attitude – and, in fact, shares it, at least to some extent. Animal studies are most useful when they illuminate clinical issues. The report in the previous issue of *Critical Care* by Bangash and colleagues is one such study [1].

Dopexamine is a dopamine analog that stimulates  $\beta$ -adrenergic and dopamine 1 and 2 receptors, conferring some vasodilatory effects. Dopexamine has classically been considered a vasoactive agent with inotropic effects, perhaps with more prominent effects in some regional vascular beds. As such, dopexamine has been tested in clinical trials to optimize hemodynamics, either in patients with shock or as part of a perioperative regimen.

## Inotropic therapy to optimize hemodynamics

The clinical benefits of inotropic therapy for hemodynamic optimization remain somewhat uncertain. Myocardial

dysfunction occurs in a subset of patients with septic shock [2], so a strategy of increasing cardiac output and thus oxygen delivery in this setting made some sense. Implementation of this strategy using dobutamine, with or without norepinephrine, to improve cardiac output to predetermined supranormal levels in all patients did not improve outcomes [3-5], and use of inotropic therapy for this purpose is not recommended in current guidelines [5]. Subsequent reports of potentially deleterious proinflammatory effects of catecholamines provided mechanistic support for their lack of efficacy when used indiscriminately [6].

## Dopexamine may be different

Use of dopexamine targeted to increase oxygen delivery to  $>600$  ml/minute/m<sup>2</sup>, however, was shown in a randomized trial reported in 1993 to decrease mortality in the perioperative period [7]. Whether this resulted from differential hemodynamic effects of dopexamine compared with other agents, perhaps selective vasodilation of regional circulations, or whether use of inotropes for perioperative optimization is different from their use in other settings was not entirely settled.

## Or is it?

Further studies since that time have advanced the field without providing complete resolution. Some reports using perioperative dopexamine found reduced morbidity or mortality [8,9], confirming the initial study, but others found no difference from conventional treatment [10-12]. A patient-level meta-analysis suggested that some of the differences might be explained by the dose of dopexamine employed [13]. Other studies indicated that dopexamine – in part due to  $\beta_2$ -adrenergic effects, but also through other pathways – might have immunomodulatory effects, especially in the spleen [14].

## Inflammation or hemodynamics?

The current study investigated both hemodynamic and inflammatory effects of a low dose of dobutamine in a rodent model of endotoxemia. Dopexamine reduced the systemic inflammatory response to endotoxin, including

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cytokine release, endothelial adhesion molecules, and oxidative stress, without substantially changing systemic hemodynamics, either blood pressure or stroke volume [1]. Regional flow, assessed by laser Doppler in the mesenteric circulation, was also not changed by dopexamine – yet lactate levels and organ function were improved [1]. The authors concluded that beneficial effects of dopexamine may result from immune modulation.

### Or both?

While immunomodulatory effects of dopexamine were demonstrated in this study, these results contrast with those of a recent clinical investigation, also carried out by this same group, in which dopexamine improved global oxygen delivery, microvascular flow and tissue oxygenation but did not change the inflammatory response to surgery [15]. Perhaps the difference could result in part from microcirculatory heterogeneity, something not assessed by the laser Doppler methodology used in this study. Previous studies have shown that regional heterogeneity may be a good predictor of outcome in shock states [16,17], and such heterogeneity might contribute to both perfusion abnormalities and production of lactate in sepsis and other inflammatory states. Thus, while this study convincingly demonstrates immunomodulatory effects of dopexamine in this model, it seems possible that microcirculatory hemodynamic effects are also playing a role.

### An integrative approach

This animal study addresses some of the mystery of why effects of dopexamine may differ from those of other catecholamines, but that mystery is not yet fully solved. Hemodynamics rule, and those who understand them rock, but this study reminds us that catecholamines have inflammatory effects that must be taken into account when considering their use. Animal studies are usually pursued as part of a reductionist approach aimed at controlling as many variables as possible in order to isolate mechanistic effects, but their interpretation and extrapolation to the clinical setting reminds us that in critical care, clinicians think of effects on different systems all together. Carefully conducted studies such as this one counteract the nihilistic tendency to think that mechanisms are too complicated and thus only hard clinical endpoints in patients are of any value, and encourage the sort of integrative approach that makes progress possible.

#### Competing interests

The author declares that he has no competing interests.

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