

## CORRESPONDENCE

and also because it was not focused on the potential side effects of the  $\alpha$ -adrenergic vasoconstrictor, such as splanchnic vascular beds. After completion of the study,<sup>1</sup> did the patients continue to receive both treatments (PhE plus inhaled NO), which resulted in a survival rate of 33.3%?

**Eric Troncy, D.V.M.**

Student

**Gilbert Blaise, M.D.**

Anesthesiologist, Associate Professor

Anesthesia Laboratory

Department of Anesthesia

CHUM

Centre Hospitalier de l'Université de

Montréal—Notre-Dame Campus

Montréal, Canada

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*In Reply:*—Thank you for the opportunity to respond to the thoughtful letter of Drs. Troncy and Blaise regarding our study.<sup>1</sup> They raise a number of valuable points as follows.

First, with regard to the effect of phenylephrine on the pulmonary vasculature, modeling of experimental data suggest that it is a result of direct vasoconstriction of small pulmonary arteries and effective enhancement of hypoxic pulmonary vasoconstriction.<sup>2</sup> As Drs. Troncy and Blaise point out, experimental data are scarce; most studies use epinephrine and norepinephrine, not phenylephrine, to explore adrenergic effects.<sup>3,4</sup> Data from cats do identify an  $\alpha$ -1-adrenergic effect of phenylephrine injected directly into

the pulmonary arterial circulation.<sup>5</sup> However, we agree that extrapolations from one species to another regarding mechanisms are necessarily speculative.

Second, we note that the definition of "response" to treatment has evolved during the years. Our definition of "responders" (increase in  $\text{PaO}_2 > 10$  mmHg) matched a criterion used by early researchers<sup>6</sup>; a ratio-based criterion (increase in  $\text{PaO}_2 \geq 20\%$ ) is now more commonly in use.<sup>7</sup> In all of our "nitric oxide responders,"  $\text{PaO}_2$  increased by at least 20%. In five of our six "phenylephrine responders,"  $\text{PaO}_2$  increased by 17–42% (mean 27%, median 25%). In the sixth patient,  $\text{PaO}_2$  increased by only 13%. By contrast, in our "phenylephrine



nonresponders," the fractional change in  $\text{PaO}_2$  varied from  $-7\%$  to  $+6\%$  (mean  $0.8\%$ , median  $1.5\%$ ). Therefore, whether reported as differences or as ratios, the  $\text{PaO}_2$  changes reveal large disparities in responsiveness to phenylephrine. The patients' responses cluster in two groups along a continuum, presumably reflecting variations in the underlying pathophysiology.

We repeated our analysis, as described previously,<sup>1</sup> counting only the five patients described herein as phenylephrine responders. Even with the smaller group, the data still showed higher  $\text{PaO}_2$  values with the combination of phenylephrine plus nitric oxide than with either treatment alone ( $P < 0.05$ ). This supports our conclusion that a subgroup of patients can be identified with a clinically significant  $\text{PaO}_2$  response to phenylephrine and that these patients will show an additional response to the combination of phenylephrine plus nitric oxide.

We agree, as we noted in our article, that our study did not have the power to identify changes in other physiologic variables (such as cardiac output) that might help to explain the  $\text{PaO}_2$  results. It is also possible that patients with sepsis might be phenylephrine "nonresponders." Our study did not address that last question, because we excluded all patients with septic physiology. We found that improvement in  $\text{PaO}_2$  with phenylephrine decreased as adult respiratory distress syndrome became more severe (negative correlation with Murray<sup>8</sup> score,  $r = 0.64$ ,  $P < 0.05$ ). The clinical status of the subject is evidently an important determinant of response to treatment, which future studies may help to elucidate.

Drs. Troncy and Blaise suggest that the large variability in baseline values of  $\text{PaO}_2$  reduced the power of our study. However, the variability was between patients not between measurements, so patterns of response to treatment could still be identified. Each patient provided a baseline before and after each measurement; patients reliably returned to their own baselines, with insignificant variation. Therefore, in analyzing the data, we were able to perform two-way analysis of variance to separate the effects of treatments from the differences between patients. (These parametric methods were warranted by the continuous nature of the data.)

We agree that our small group and even smaller subgroups do not constitute a statistically powerful sample. However, our results convince us that phenylephrine improves oxygenation in certain patients and that these improvements may be additive or synergistic with the effects of nitric oxide. This conclusion

warrants further study in a larger population to explore the magnitude of the effects and their potential therapeutic usefulness.

**Elana B. Doering, Ph.D., M.D.**

Department of Anesthesiology  
College of Physicians and Surgeons of Columbia University  
New York, New York

**C. William Hanson, M.D.**

Department of Anesthesia

**Carol Marshall, Ph.D.**

**Bryan E. Marshall, M.D.**

Center for Research in Anesthesia

Hospital of the University of Pennsylvania  
Philadelphia, Pennsylvania

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