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Phenylephrine and Inhaled Nitric Oxide

To the Editor:—Having read the study of Doering *et al.*¹ with great interest and because of our experience of using phenylephrine (PhE) and inhaled nitric oxide (NO) in experimental conditions² and inhaled NO in patients,³ we would like to moderate the conclusions of the authors¹ and of the accompanying editorial⁴ and propose a different hypothesis.

In the introduction, Doering *et al.*¹ report that "Phenylephrine, an α -receptor agonist, has pulmonary and systemic vasoconstrictor effects," referring to the review of Dawson.⁵ In this particular article,⁵ the pulmonary vasoconstriction in response to sympathetic stimulation concerns mainly the use of norepinephrine, epinephrine, and electrical stimulation (not PhE) in precise species, *i.e.*, dog, cat, and rabbit. However, species differences have been reported in the noradrenergic innervation of the pulmonary artery and its branches.⁶ The sheep, guinea-pig, rabbit, feline, and canine pulmonary arteries have a rich density of α -adrenergic receptors, whereas calf, rat, and swine pulmonary arteries have a sparse distribution.⁷ Because the pig has a cardiopulmonary physiology, pharmacology, and anatomy comparable in many respects to that of humans,⁸ we studied the mechanism of PhE-induced pulmonary hypertension in swine. During the experiment,² the pulmonary vascular resistance (PVR) did not change, in agreement with the heterogeneous,⁹ sparse, or nonexistent⁶ α -adrenergic innervation of the swine pulmonary resistance vessels. In humans, controversy exists concerning the effects of α -adrenergic agonists on the pulmonary vascular bed.¹⁰ In healthy humans, if the pressor response to acute hypoxia arose from an increased PVR, the pressor response to norepinephrine infusion is translated primarily into "back pressure" from the left side of the heart (*i.e.*, without an increase in PVR).¹¹ Results were almost identical in patients with pulmonary hypertension.¹² Finally, humans and pigs present the same intermediate magnitude of vasoconstrictor response to acute hypoxia¹⁰ by the so-called phenomenon of hypoxic pulmonary vasoconstriction (HPV).¹³

PhE induced no change in heart rate, cardiac output (CO), PVR, and venous admixture (Q_{VA}/Q_T) in acute respiratory distress syndrome (ARDS) patients¹ and experimental pigs.² We noted, particularly in the selected group of PhE-responders, an increase in pulmonary artery pressure (mPAP from 30 ± 2 mmHg to 32 ± 2 mmHg) and a statistically nonsignificant increase in pulmonary artery occlusion pressure by PhE (from 13 ± 1 mmHg to 16 ± 2 mmHg).¹ These results correlate well with the increases in mean pulmonary arterial pressure, pulmonary artery occlusion pressure, left atrial pressure (LAP), and central venous pressure (CVP) that we observed with PhE in healthy pigs.² Here¹ measurements of central venous pressure were recorded but not shown. Because of these results, it seems difficult to call PhE "an intravenous pulmonary vasoconstrictor,"¹⁴ and it would be better to consider the mechanism of PhE action not only as a potentialization of hypoxic pulmonary vasoconstriction,¹⁴ but also as a reduced compliance of left ventricular filling induced by the increased systemic afterload,

which is passively reflected on the pulmonary vascular bed. This hypothesis, in relation with the high variability in the presence of α -adrenergic receptors on human pulmonary arteries, would bring an element of response to "the reasons why some but not all patients respond to PhE."¹⁴ These latter have necessitated higher doses of PhE for the same level of increase in mean systemic arterial blood pressure (mABP) than the PhE-responders. Was this in relation with their sepsis status associated with high production of NO making them less sensitive to catecholamines? In our study of healthy pigs,² PhE did not affect gas exchange parameters. In the study of Doering *et al.*¹ with ARDS patients, PhE increased oxygenation in some patients and showed an evident synergistic effect with inhaled NO in this parameter.

The authors¹ opted for a definition of NO-responders (increase > 10 mmHg in Pa_{O_2}), which is not frequently found in the literature (4 times in 19 publications), as recently reviewed by our group.¹⁶ Using a 10-mmHg increase in Pa_{O_2} as the limit allowed the authors to sequence the data in two equal ($n = 6$) groups of PhE responders and PhE nonresponders. However, most of the authors accept as a criterion for NO responder an increase in hypoxia score (Pa_{O_2}/Fi_{O_2}) of more than 20%.^{3,14-16} In this instance, the authors¹ would not obtain a rate of 11 per 12 and 6 per 12 for NO and PhE responders, but probably of 7 per 12 and 2 per 12, respectively, as estimated from Fig. 1.

Inhaled NO seemed to be acting on oxygenation by the classic steal phenomenon, described in the literature for ARDS patients,¹⁴ for the PhE nonresponders but not for the PhE responders (no effect on mean pulmonary arterial pressure, PVR, cardiac output, pulmonary artery occlusion pressure, and venous admixture [Q_{VA}/Q_T]). We observed that cardiac output tended to increase in these patients, partially explaining the improved oxygenation, as also observed with concomitant use of inhaled NO and permissive hypercapnia.¹⁷

The statistical analysis was confusing (with the use of two types of statistical analyses, *i.e.*, parametric and nonparametric, for different variables), and the results obtained were not homogeneous (statistical significance observed for mean systemic arterial blood pressure with PhE alone but not for PhE plus inhaled NO in tables 2 and 3 of the article by Doering *et al.*, even if the differences and variabilities were similar in both conditions). We agree with the authors' prudence about the limited power of their statistical analysis.

Even if the authors¹ were prudent about the weight given to their results, it is true that the presented analysis has many shortcomings. Finally, its association with such an editorial,⁴ based on future, positive possibilities of concomitant therapy with inhaled NO and PhE, looked quite dangerous because we are not convinced by the ability of PhE to (1) increase oxygenation in ARDS patients; (2) convert inhaled NO nonresponders to NO responders; and (3) improve the outcome of ARDS patients in synergism with inhaled NO, particularly because of the drawbacks of the study¹

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

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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.¹ 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.² As Drs. Troncy and Blaise point out, experimental data are scarce; most studies use epinephrine and norepinephrine, not phenylephrine, to explore adrenergic effects.^{3,4} Data from cats do identify an α -1-adrenergic effect of phenylephrine injected directly into

the pulmonary arterial circulation.⁵ 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 researchers⁶; a ratio-based criterion (increase in $\text{PaO}_2 \geq 20\%$) is now more commonly in use.⁷ In all of our "nitric oxide responders," PaO_2 increased by at least 20%. In five of our six "phenylephrine responders," PaO_2 increased by 17–42% (mean 27%, median 25%). In the sixth patient, PaO_2 increased by only 13%. By contrast, in our "phenylephrine