

# Vasopressin

## The Perioperative Gift that Keeps on Giving

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**T**HE pulmonary circulation is distinct from the systemic circulation both in structure and in function. Pharmacologic options for selective therapeutic manipulation of pulmonary vascular tone are limited. A major clinical milestone in contemporary perioperative practice has been the advent of selective pulmonary vasodilators that have transformed the management of pulmonary hypertension and right ventricular dysfunction both in the operating room and in the intensive care unit. The pulmonary vasodilators come in intravenous (e.g., prostacyclin), inhalation (e.g., nitric oxide), and oral preparations (e.g., sildenafil). In contrast, clinical vasoconstrictor agents have remained relatively nonselective. Most pharmacologic agents for support of systemic vascular tone increase pulmonary vascular resistance whether desired or not.

This therapeutic gap has been studied and it appears that not all intravenous vasoconstrictors lack specificity for the systemic vascular bed. The vasobiology of vasopressin has been studied in this issue of *ANESTHESIOLOGY*. Currigan *et al.* have demonstrated that vasopressin, an established systemic vasoconstrictor, has minimal effect on pulmonary vascular tone.<sup>1</sup>

In their *in vitro* study utilizing isolated human pulmonary and radial artery ring segments, the investigators demonstrated that phenylephrine, metaraminol, and norepinephrine significantly constricted both the pulmonary and radial arteries – a finding consistent with our current understanding of conventional  $\alpha$ -adrenoreceptors. Vasopressin, however, in this laboratory model, was a potent constrictor of the radial artery but exerted no significant effect on the pulmonary artery – this is, to the best of our knowledge, the



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patients with pulmonary hypertension or right ventricular dysfunction, vasopressin is preferred to other vasoconstrictors since it can selectively support systemic vascular tone without increasing pulmonary vascular resistance and right ventricular afterload.

Vasopressin provides a dual benefit to the failing right ventricle. Initially, the increased systemic vascular tone increases coronary perfusion pressure to increase myocardial oxygen delivery. Also, the increased oxygen supply due to increased coronary perfusion pressure is not at a cost of increasing right ventricular afterload. Consequently, in

first time that this selective vasoconstrictor effect of vasopressin has been demonstrated in human tissue at the bench.

What are the implications of this seminal observation for the practicing clinician in the perioperative clinical arena? Vasopressin is already established as a systemic pressor in advanced vasoplegic states associated with cardiopulmonary resuscitation, sepsis, anaphylaxis, liver transplantation, cardiopulmonary bypass, and pheochromocytoma resection.<sup>2,3</sup> Vasopressin is often the “go-to” drug of choice in the treatment of refractory hypotension due to catecholamine-resistant shock.<sup>3</sup> The study by Currigan *et al.* further supports the use of vasopressin in the setting where increasing pulmonary vascular tone may be deleterious (e.g., acute right ventricular dysfunction). Currigan *et al.* provide *in vitro* evidence of yet another gift—that vasopressin is a selective systemic vasoconstrictor in human vascular rings, and therefore, if this effect occurs *in vivo*, it would spare the right ventricle of the deleterious effects of pulmonary vasoconstriction. In

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combination with an inhaled selective pulmonary vasodilator, vasopressin advances the perioperative management of clinically significant pulmonary hypertension and right ventricular dysfunction. This dual drug strategy for the failing right ventricle can be considered a 'pharmacologic balloon pump' for the failing right ventricle – analogous to intra-aortic balloon counterpulsation that mechanically supports the failing left ventricle with both enhanced oxygen delivery from coronary perfusion pressure augmentation during diastole and reduced oxygen demand from decreased afterload during systole. Further trials should explore whether this pressor selectivity of vasopressin results in better perioperative outcomes in high-risk patient populations.

Where do we go from here? Our understanding of the unique vascular biology of the lung can be expanded by defining the effects of vasopressin on pulmonary vascular tone yet further. The limitations of the work by Currigan *et al.* provide direction for future avenues of research. The study utilized segments of large-diameter human pulmonary artery that are not the resistance vessels of the pulmonary circulation. It remains unclear whether the response to vasopressin would be identical or different in the more distal, resistance arterioles of the pulmonary circulation. The study was carried out under normoxic conditions – the question arises whether powerful determinants of pulmonary vascular tone such as hypoxia or hypocarbia would alter the pressor response of the pulmonary artery to vasopressin? Furthermore, one wonders how the effects of vasopressin on pulmonary vascular tone may vary *in vivo*, given the powerful influence of autonomic regulation and hypoxic pulmonary vasoconstriction. The study utilized adult pulmonary artery samples from patients undergoing lung resection. To what extent does maturation of the pulmonary circulation play a role in its response to exogenous agents? Pulmonary vasoconstriction becomes especially problematic in the pediatric patient with congenital heart disease and the inferences of the Currigan *et al.* work may not apply to this cohort. The study took specimens from a small number of patients to analyze *in vitro*. Pharmacogenomics often suggests a large range of responses to a medication necessitating a much larger sample to reliably estimate an effect. Hence, it is somewhat of a leap to apply the effects recorded in a small sample to the general population with respect to the pulmonary artery. Examination of vasopressin in a much larger sample size, in patients with different comorbidities and demographics, and under various conditions, is necessary to confidently move forward with the expectation that vasopressin spares the pulmonary circulation in the treatment of catecholamine-resistant systemic vasodilatation.

Opportunities also exist in the study of select vasoconstrictors in other organ systems. Vasopressin has a role in the medical control of upper gastrointestinal bleeding – in

fact, the norepinephrine-sparing effects of vasopressin in a patient with gastrointestinal bleeding and vasodilatory shock encouraged Professor Donald W. Landry, M.D., Ph.D. at Columbia University in New York to explore the mechanistic basis for vasopressin in this setting yet further (verbal communication in April 2002). The Landry work was begun in the 1990s and is now well accepted in the management of vasopressin deficiency and systemic vasoplegia.<sup>3</sup> This astute observation at the bedside sparked a clinical innovation and changed our understanding of vasopressin physiology.

Could there be surprising and therapeutically important effects of vasopressin in the vasobiology of pregnancy or neurological disease? Given the ongoing surprises with vasopressin to date, these questions merit further scientific inquiry. What are the effects of vasopressin on uterine blood flow at various stages in pregnancy? What are the effects of vasopressin on cerebral and spinal cord blood flow? How are the effect of vasopressin influenced by known regulators of cerebral blood flow such as carbon dioxide, anesthetic agents and intracranial hypertension? Does vasopressin offer advantages in the conduct of spinal cord rescue after reconstruction of the thoracoabdominal aorta? These questions represent major research opportunities both within and beyond our specialty.

Finally, Currigan *et al.* are to be congratulated for their landmark study that highlights yet another unique aspect about vasopressin, the gift that keeps on giving to our specialty. Their astute bench observation suggests multiple avenues of future scientific investigation. It is likely that vasopressin can still keep on giving us more therapeutic options to make the perioperative period even safer for our patients.

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