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EDITORIAL

Boosting systemic pressure with phenylephrine: arterial or venous modulation?

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Given that systemic circulation is a closed-loop system, the mean left ventricular (LV) cardiac output (CO) is equal to the systemic venous return. In this regard, both volume expansion and vasopressors are used to maintain vital organ perfusion pressure. The vast majority of haemodynamic studies evaluating the effects of inotropes and vasopressors on blood circulation have focused on cardiac performance and arterial tone without systematically assessing the role of venous return [1]. A more realistic conception of the positive effect of vasopressors on CO during hypovolemia is to consider the role of these agents on the venous system (enhancement of venous return via venoconstriction) rather than on ventriculo–arterial coupling [1].

Phenylephrine is a pure alpha-adrenergic receptor agonist that is widely used in the operating room to restore arterial pressure in anaesthesia-induced hypotensive patients [2]. The effects of phenylephrine on CO are complex, poorly understood and difficult to predict. In theory, alpha-adrenergic receptor agonists may have opposite effects on venous return. On the one hand, they decrease venous capacitance, which in turn increases venous return. On the other hand, alpha-adrenergic receptor agonists also increase the resistance to venous return, which consequently decreases venous return [3]. Thus, phenylephrine may either increase or decrease CO in patients with preload reserve [4]. Moreover, the phenylephrine-induced increase in LV afterload might decrease CO, especially in cases of impaired cardiac contractility [5].

In this issue, Kalmar et al. elegantly depicted the chronology of the haemodynamic effects, caused by a single administration of phenylephrine, in preload-dependent patients with anaesthesia-induced hypotension. For this purpose, the authors assessed several distinct haemodynamic and non-haemodynamic indices [6]. They showed that phenylephrine administration resulted in an increase in cardiac preload, as illustrated by the decrease of both static and dynamic markers of cardiac preload, which increased CO despite the increase in LV afterload, reflected by an increased systemic vascular resistance [1]. The authors suggest the increase in cardiac preload to be the result of an increase in venous return, as they found the pressure gradient driving the venous return to be increased to a greater extent than the resistance to the venous return [6, 7].

Thus, phenylephrine would increase CO in patients with preload reserve by redistributing venous blood from the unstressed to stressed volume [1]. Interestingly, the authors confirm that recruiting blood from the venous territory, using phenylephrine, increases cardiac preload and stroke volume, thereby diminishing preload dependency and dynamic indices. Similarly, it has been previously shown that in septic shock patients, the administration of norepinephrine, another alpha-adrenergic receptor agonist, increased cardiac preload and CO [8, 9], while reducing the degree of preload dependency [7, 9]. For phenylephrine, other studies found that the norepinephrine-induced changes in cardiac preload and CO were determined by the respective changes in mean systemic filling pressure and resistance to venous return [10, 11].

Nevertheless, the interesting results presented by Kalmar et al. should be interpreted with caution. In their study,

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mean systemic filling pressure and all derived parameters of venous return were estimated from a mathematical algorithm, including CO, mean arterial pressure and central venous pressure measurements [6]. This approach results in an obvious mathematical coupling between the changes in CO and changes in the parameters describing the venous return. It would have been interesting to investigate the effects of phenylephrine on venous return, independently from CO. For this purpose, two other bedside methods are currently available. The first one, taking into account Guyton's approach of venous return, is based on the haemodynamic effects of heart–lung interactions and requires the performance of end-expiratory [12] or combined end-expiratory and end-inspiratory holds [10]. The second method estimates mean systemic filling pressure from the transient stop-flow in the upper arm [12]. Thus, haemodynamic effects of phenylephrine should be further confirmed by using multimodal haemodynamic monitoring, including indices of cardiac preload, afterload and contractility that are assessed independently from each other. Moreover, the authors used an uncalibrated pulse-contour analysis to measure CO. Unfortunately, this technique is known to suffer from inaccuracy when acute afterload increases occur.

The authors attribute the observed decrease in pulse pressure variations (PPV) to a right-shift of the heart on the Frank–Starling curve and thus a transition from a preload responsive state to a fluid unresponsive state (although the patients had not received fluids). The authors interpret these findings as an auto-transfusion phenomenon, resulting from the recruitment of unstressed volume, caused by venous vasoconstriction. However, this assumption may be too trivial. Another way for vasopressors to influence PPV is by directly reducing arterial vascular compliance, also resulting in an increase in PPV [13]. Since vasopressors have a direct effect on both regional vascular capacitance (i.e., venous return) and arterial compliance, these drugs may decrease and increase PPV at the same time.

The knowledge of the pharmacological and physiological effects of vasopressors is very complex and can only be elucidated using a variety of sophisticated techniques. The interpretation of the circulatory physiology in the individual patient remains a fascinating challenge at bedside. Growing evidence points at the important role of venoconstriction to enhance blood flow and corroborates the theory that the pooled venous compartment is a key determinant of the effects of alpha-adrenergic receptor agonists on systemic arterial pressure.

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