already available from some TCI pump manufacturers for clinical use. However, we believe that there is still more work to be done to validate and compare these different models clinically when they are used for titration to a specific effect, before we discard older models for one 'ultimate' model,[9] particularly if a model developed for a specific subgroup performs significantly better during titration. An alternative approach is to have the pump use the 'best' model for a child, an adult, or an obese adult after the patient covariates have been entered. A potential advantage of this latter approach is that it is easy to accommodate a future model developed for a specific subgroup without requiring yet another analysis of an increasingly larger data set.

We thank Vellinga and colleagues[1] for investigating this important topic and for their contribution to ongoing research into the clinical validation and comparison of different PK/PD models and their performance during titration to a desired clinical effect using TCI.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Relationship between variations in cardiac output and end-tidal CO_2 after phenylephrine infusion in anaesthetised patients

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Editor—Several studies have highlighted a strong relationship between perioperative hypotension and adverse postoperative outcomes (acute kidney injury, myocardial ischaemia, and stroke).[1] Treatment options most commonly used to manage intraoperative hypotension are volume expansion and vasopressors. Phenylephrine, a pure α-adrenergic receptor agonist with α_1 and α_2 actions, is commonly used in this context with well-known haemodynamic effects on arterial pressure, systemic vascular resistance, and left ventricular afterload. However, the effects of phenylephrine on cardiac output (CO) are variable and remain debated. On the one hand,

phenylephrine can decrease CO in patients who are preload-dependent, have impaired cardiac contractility by increasing left ventricular afterload, or both. On the other hand, phenylephrine-induced vasoconstriction can increase cardiac preload and then stroke volume.[2] Unfortunately, CO is not routinely monitored in the operating room,[3] and significant changes in CO can therefore be undetected. Several studies suggest that changes in end-tidal carbon dioxide (CO_2) concentration ($EtCO_2$) can reflect an increase in CO induced by intravascular volume expansion.[4] Physiologically, when alveolar ventilation and CO_2 production are constant, changes in $EtCO_2$ can accurately reflect changes in CO. However, whether changes in $EtCO_2$ can be used to track a decrease in CO in patients receiving phenylephrine is not known. The aim of the present study was to evaluate the ability of changes in $EtCO_2$ to identify reductions in CO $\geq$10% after phenylephrine administration.[5]

We conducted a secondary analysis of data from a recent multicentre study,[6] in which 56 patients without major cardiovascular or respiratory disease undergoing neurosurgery or digestive surgery were prospectively enrolled. Induction of anaesthesia used propofol and remifentanil or sufentanil, and general anaesthesia was maintained by continuous infusion of propofol or inhaled sevoflurane with analgesia by continuous remifentanil infusion or discontinuous sufentanil infusion. Patients were ventilated by volume-controlled mode with a tidal volume of 6–8 ml kg^{-1} of predicted body weight and positive expiratory pressure of 6–10 cm H_2O. Oxygen saturation was maintained >96% and ventilatory frequency was adjusted to achieve an $EtCO_2$ of 4–4.6 kPa. Anaesthesia and ventilator settings were kept unchanged during the procedure. Arterial pressure was monitored using a radial arterial catheter, and CO was assessed using oesophageal Doppler (CardioQ ODM+, Deltex Medical, Chichester, UK). The $EtCO_2$ was monitored with a sensor linked to the tracheal tube and connected to the ventilator, which allowed analysis of expired gas samples and instantaneously displayed $EtCO_2$ in mm Hg. Two sets of measurements were recorded: (1) immediately before administration of a 50 μg bolus of phenylephrine i.v. and (2) 3 min later (when MAP was restored, with variations <5% for 1 min). Phenylephrine was administered for MAP <65 mm Hg.

Of 35 women and 21 men included, the mean age was 57 (13) yr; 17 (30%) patients had preoperative hypertension. All patients received at least one fluid challenge (250 ml of NaCl 0.9%) before phenylephrine administration. Phenylephrine induced a significant decrease in CO (≥10% decrease) in 46 patients (82%) and a significant increase (≥10% increase) in CO in one patient. Individual changes in CO are shown in Figure 1. The haemodynamic effects of phenylephrine administration are shown in Table 1. Changes in CO and changes in $EtCO_2$ after phenylephrine infusion were poorly correlated (r^2=0.08, P=0.03). Phenylephrine-induced changes in $EtCO_2$ were not able to identify a significant decrease in CO (area under the receiver characteristics curve [AUROC]=0.586 [0.110]; P=0.44).

This secondary analysis highlights two major points: (1) administration of phenylephrine in patients who have previously received volume expansion was associated with a decrease in CO in 82%, and (2) changes in $EtCO_2$ were not able to identify decreases in CO after phenylephrine infusion. The

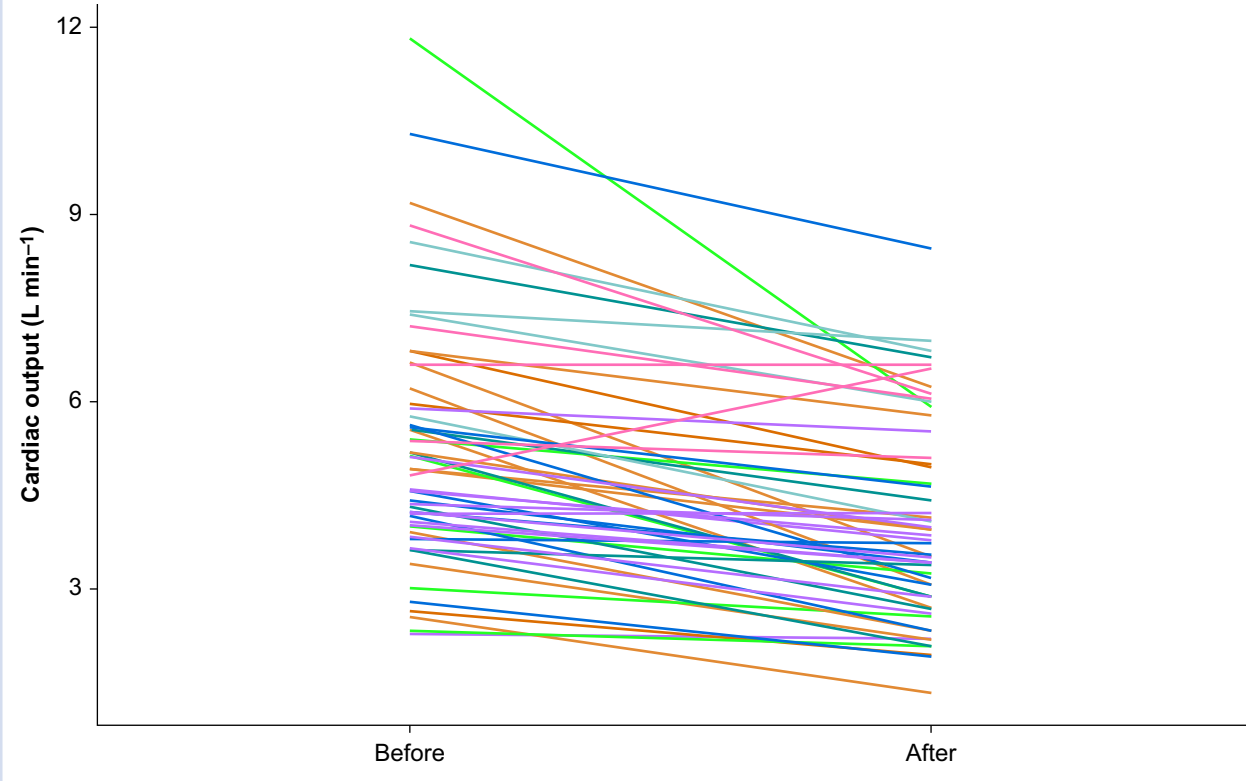

Fig 1. Individual changes in cardiac output induced by infusion of phenylephrine (50 μg i.v.).

Table 1 Haemodynamic variables before and after phenylephrine infusion in patients based on changes in cardiac output. Values are expressed as median [percentile, 25–75]. P, difference between before and after phenylephrine infusion (Wilcoxon test); $EtCO_2$, end-tidal carbon dioxide; PE, phenylephrine; PPV, pulse pressure variation; SVV, stroke volume variation.

	Overall population (n=56)			Decrease in CO ≥10% (n=46)			CO decrease <0% or increase (n=10)		
	Before PE	After PE	P-value	Before PE	After PE	P-value	Before PE	After PE	P-value
Heart rate (bpm)	60 [56–71]	57 [52–65]	<0.0001	60 [55–72]	56 [50–61]	<0.0001	61 [56–67]	63 [56–71]	0.2
Systolic arterial pressure (mm Hg)	80 [77–87]	102 [93–115]	<0.0001	80 [77–96]	102 [92–113]	<0.0001	86 [80–91]	102 [97–120]	0.002
MAP (mm Hg)	60 [55–64]	75 [69–85]	0.0001	60 [55–63]	75 [69–86]	<0.0001	61 [56–67]	63 [56–71]	0.25
Cardiac output (L min^{-1})	4.9 [4.0–6.1]	3.7 [2.9–5.1]	<0.0001	5.0 [4.0–6.2]	3.5 [2.7–4.7]	<0.0001	4.6 [3.8–5.9]	4.6 [3.7–6.5]	0.20
Stroke volume (ml)	81 [66–96]	64 [55–82]	<0.0001	84 [66–97]	63 [53–81]	<0.0001	74 [62–88]	77 [60–91]	0.73
PPV (%)	9 [6–11]	6 [4–9]	<0.0001	8 [6–10]	5 [4–9]	<0.0001	11 [8–12]	8 [6–8]	0.01
$EtCO_2$ (mm Hg)	30 [28–32]	30 [29–33]	0.01	30 [28–32]	30 [29–32]	0.05	31 [26–32]	31 [27–33]	0.15
SVV (%)	14 [10–16]	11 [8–15]	0.0005	14 [10–16]	11 [8–14]	0.0009	14 [10–21]	13 [8–18]	0.234

effects of phenylephrine on CO are not clearly established. Several studies have shown a decrease in CO that is more pronounced in patients who are preload-dependent.[2] However, recent work has suggested that phenylephrine may lead to an increase in CO.[7] These results should be weighed against the fact that the CO monitoring device used in this work is very sensitive to vasomotor tone and vasopressor injection.[8] This may have led to errors in CO measurements during vasopressor administration.

In clinical settings, it is not obvious that changes in $EtCO_2$ reflect changes in CO. Some studies have identified correlations between changes in CO and variations in $EtCO_2$ after 500 mL volume expansion or passive leg raising in the ICU and in the operative room, but this is not supported by other studies.[9,10] The ability to identify a vasopressor-induced decrease in CO is of major importance in clinical practice. Unfortunately, the present analysis does not support the use of changes in $EtCO_2$ in this setting.

In conclusion, our results suggest that in patients who have received intravascular volume expansion, phenylephrine administration is frequently associated with a reduction in CO and that, in this clinical situation, changes in $EtCO_2$ failed to detect changes in CO.

Declarations of interest

MB received honoraria from Edwards Lifesciences (Irvine, CA, USA) and Pulsion Medical System (Munich, Germany) for lectures. EF received honoraria from Dräger and GE Healthcare for lectures. The other authors declare no competing interests.

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