EJA

Eur J Anaesthesiol 2020; **37**:159–161

EDITORIAL

Is goal-directed haemodynamic therapy dead?

Simon Gelman

European Journal of Anaesthesiology 2020, **37**:159–161

Goal-directed haemodynamic therapy (GDHT) employs periodic (or continuous) measurement of cardiac output (CO) or a surrogate such as stroke volume variations to assess fluid responsiveness. Specifically, if a small amount of fluid infusion is associated with an increase in CO, the infusion should be continued. If an increase in CO does not follow a test infusion, the infusion could be stopped.

Some studies of GDHT have demonstrated an improved outcome following surgical procedures, but many others failed to support such a conclusion. A relatively recent review based on analyses of more than 12 000 patients concluded that 'the most effective GDHT strategy remains unclear'.[1] In addition, it was noticed that fluid responsiveness was observed only in approximately half of the patients undergoing GDHT.[2,3]

The relevant question at this point had to be what comes next, should the GDHT concept be allowed to die from the lack of effectiveness, or should we seek a possible improvement in the methodology. To address this dilemma, we need to understand the physiology around the failure of response to fluid therapy, and, indeed, there has been a recent attempt to do this.[4]

One condition that might interfere with fluid responsiveness is insufficient pump function of the heart. Amongst reasons for deterioration of heart pump function are decrease in myocardial contractility, arrhythmia, compression of the heart and large vessels by cardiac tamponade, increase in intrathoracic pressure and perhaps some others. We have learned more or less how to diagnose such conditions.

Severe hypovolaemia might lead to a situation where small amounts of infused fluid (the test dose) fail to significantly change any variables dependent on volume.

Finally, a group of phenomena may be associated with change in the relationship between stressed and unstressed intravenous volumes, V_s and V_u, respectively. Any vasodilation (actually veno-dilation) leads to an increase in V_u and thereby to a decrease in V_s with the physiological consequences of hypovolaemia. Any veno-constriction in conditions of total normo-volaemia means a decrease in V_u that leads to an increase in V_s, leading to an increase in venous return and CO. The recently published study by Nakamoto *et al.*[5] has addressed this issue. The idea behind the current study was to decrease the V_u by using a vasoconstrictor, and thereby to increase the V_s.[5] An increased or maintained V_s should help to avoid administration of excessive fluid, often used to counteract the vasodilation (an increase in V_u) induced by the anaesthetic. To conduct GDHT in conditions of vasopressor infusion, we need to know how vasopressors affect fluid responsiveness. The main achievement of this study is the demonstration that fluid responsiveness is not only preserved but actually is increased during vasopressor therapy.

We may speculate that the smaller the V_u, the less fluid is needed to induce changes in the transmural pressure and in the V_s. In other words, a decrease in V_u should increase the sensitivity of the cardio-vascular system to the fluid challenge. The results of the study by Nakamoto *et al.*[5] support such speculations.

The detailed definitions and physiological meaning of the involved variables are available elsewhere.[4,6–8] Here I would like to emphasise that the only difference between the V_u and V_s is that the V_s is the volume of blood under transmural pressure above zero while V_u is a blood volume under transmural pressure equal to zero. The blood flow within a vein is generated by the transmural pressure. As the V_u is at zero pressure by definition, the flow at this moment in this vein is close to zero. This means that V_s is actively involved in haemodynamic status, while V_u is not. When we say that a patient is clinically hypovolaemic, we mean that the V_s is decreased. What is happening with V_u at that moment is irrelevant to haemodynamic status, but may be very important at a

From the Department of Anaesthesiology, Peri-operative and Pain Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence to Simon Gelman, MD, PhD, Department of Anesthesiology, Peri-operative and Pain Medicine, Brigham and Women's Hospital 75 Francis Street, Boston, MA 02115, USA
Tel: +1 617 732 8280; fax: +1 617 264 5230; e-mail: sgelman@bwh.harvard.edu

DOI:10.1097/EJA.0000000000001118

time when V_s is decreased and there is a need to convert a part of V_u into the V_s to correct clinical hypovolaemia. The values of the V_u and V_s are virtual, there are no chambers or membranes between the two, but the volumes can and do convert from V_u to V_s and vice versa under the influence of different insults.

Anaesthetics (or analgesics, or any vasodilating drugs, or withdrawal from vasoconstricting influences) dilate compliant veins, leading to an increase in V_u, a decrease in V_s and arterial hypotension. The latter is often treated with fluid infusion. The infused fluid first increases the V_u because the transmural pressure is lower than in V_s. When the transmural pressure in V_u increases above zero, this volume becomes the V_s. Restoration of the V_s restores the haemodynamic responses. Later, during the postoperative period, when venous tone comes back to baseline, V_u decreases, converting blood into V_s, with the risk of overload. This may be responsible for the lack of effectiveness of the GDHT in many cases.

Let us assume a very compliant venous wall and let us consider the infusion of fluid into such a vein. At the beginning of the infusion, a compliant vein would be stretched very little and a transmural pressure above zero would not be generated; if the infusion is continued, the situation would reach a point which may be called the point of V_u-to-V_s conversion. There is no change, neither in the vein nor the blood within it, but beyond the conversion point when the transmural pressure increases, the volume of blood within it becomes stressed by higher transmural pressure. At that moment, this volume is already V_u and flow is generated. The higher the pressure, the higher the flow, within certain ranges. These relationships are brought in to play during GDHT.

Infusing small doses of vasopressors decreases the V_u, which does not contribute to haemodynamic status, and increases the V_u without changing total volume. This would allow infusion of smaller amounts of fluid but with the same haemodynamic effect. This is exactly what the study by Nakamoto *et al.*[5] showed: the infused vasopressor to a certain end point was associated with a decrease in fluid requirement, a decrease in blood loss and requirement for transfusion, and a decrease in the number of infused boluses of fluid. This is all good.

The potential problem to be considered is that the vasopressor may constrict arteries and jeopardise tissue perfusion and might eliminate the symptoms that we usually use to suspect and diagnose hypovolaemia, possibly both.

As the density of α-1 adrenergic receptors is much higher in veins than in arteries (therefore the veins are much more sensitive to the α-adrenergic agonists than arteries),[9,10] there must be doses of the drugs that would constrict mainly veins, not arteries. In addition, constriction of arteries may decrease the blood flow and lead to tissue hypoxia, while constriction of compliant veins leads to a shift of blood volume downstream towards the heart, increasing venous return and CO. All this makes the probability of tissue hypoxia in the conditions described in the study unlikely.

Another reasonable concern is whether the infusion of vasopressors changes the haemodynamic responses and interferes with diagnosis of hypovolaemia. Nakamoto *et al.*[5] showed that fluid responsiveness is preserved, even enhanced, in the conditions created by the doses of vasopressors used. That is a very important observation because it suggests that our diagnostic tools are not eliminated by vasopressors when used in the doses documented by this study.

Phenylephrine and norepinephrine exert a vasoconstricting effect on arteries and veins via α-1 adrenergic receptors. But norepinephrine, through its activation of β-2 adrenergic receptors, also produces vasodilation. The situation is even more complex because the activation of β-2 adrenergic receptors is associated with an increase in release of norepinephrine[11,12] and angiotensin.[13] Moreover, stimulation of α-1 receptors may constrict hepatic veins impeding the flow through the splanchnic system and leading to sequestration of some blood within the liver and a decrease in venous return and CO.[12,14] All this may make the interpretation of the observed event quite difficult.

The observation in the study by Nakamoto *et al.*[5] that phenylephrine infusion was associated with higher values of CO probably resulted from the shift of blood volume from compliant veins into systemic circulation. The observed ability to further increase CO in the study suggests that the small dose of phenylephrine did not empty splanchnic compliant veins completely.[5] Therefore, presumably, the V_u decreased but not emptied and some V_u was preserved.

The observer believes that the study by Nakamoto *et al.*[5] will lead to many further investigations that would test the hypotheses concerning the basic characteristic of the drugs in question and the doses of vasopressors that can be safely and beneficially given to our patients.

So, the response to the question posed in the title of this Editorial is negative because Nakamoto *et al.* have shown the way to further explore the possibility of improving the results of GDHT.[5]

Acknowledgements relating to this article

Assistance with the Editorial: none.

Financial support and sponsorship: none.

Conflicts of interest: none.

Comment from the Editor: this Editorial was checked by the editors but was not sent for external peer review.

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