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EDITORIALS

Intraoperative hypotension is just the tip of the iceberg: a call for multimodal, individualised, contextualised management of intraoperative cardiovascular dynamics

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Overall mortality in the first weeks *after* inpatient surgery remains high.[1] The risk for postoperative death depends on a multitude of factors, including patient-related factors, such as age and co-morbidities, and surgery-related factors. Postoperative complications are associated with postoperative deaths.[1] Major surgery under general anaesthesia induces marked alterations in cardiovascular dynamics. Alterations in cardiovascular dynamics, in turn, may lead to impaired perfusion of vital organs, and thus may be associated with postoperative complications.[2,3] Therefore, optimisation of global cardiovascular dynamics to maintain or restore tissue perfusion and oxygenation is a promising concept to improve postoperative outcome in patients having surgery.[4]

In this context, intraoperative hypotension has received a lot of attention in the scientific literature.[5,6] Intraoperative hypotension is common in patients having noncardiac surgery under general anaesthesia, and large cohort studies have shown an *association* between the severity and duration of intraoperative hypotension and myocardial injury, acute kidney injury, and death.[5,7] Thus, identifying, treating, or even preventing intraoperative hypotension as a modifiable risk factor for adverse postoperative outcomes is clinically plausible and important.[5,6]

Intraoperative hypotension, however, might be just the tip of the iceberg that we see because arterial pressure is measured ubiquitously during surgery. Intraoperative hypotension is one of many signs reflecting profound alterations in cardiovascular dynamics, with some other signs rarely recognised because they are not monitored or simply ignored. Therefore, 'sensitive, specific, and continuous measures of cellular function to evaluate arterial pressure management in a physiologically coherent manner' need to be developed.[6] We

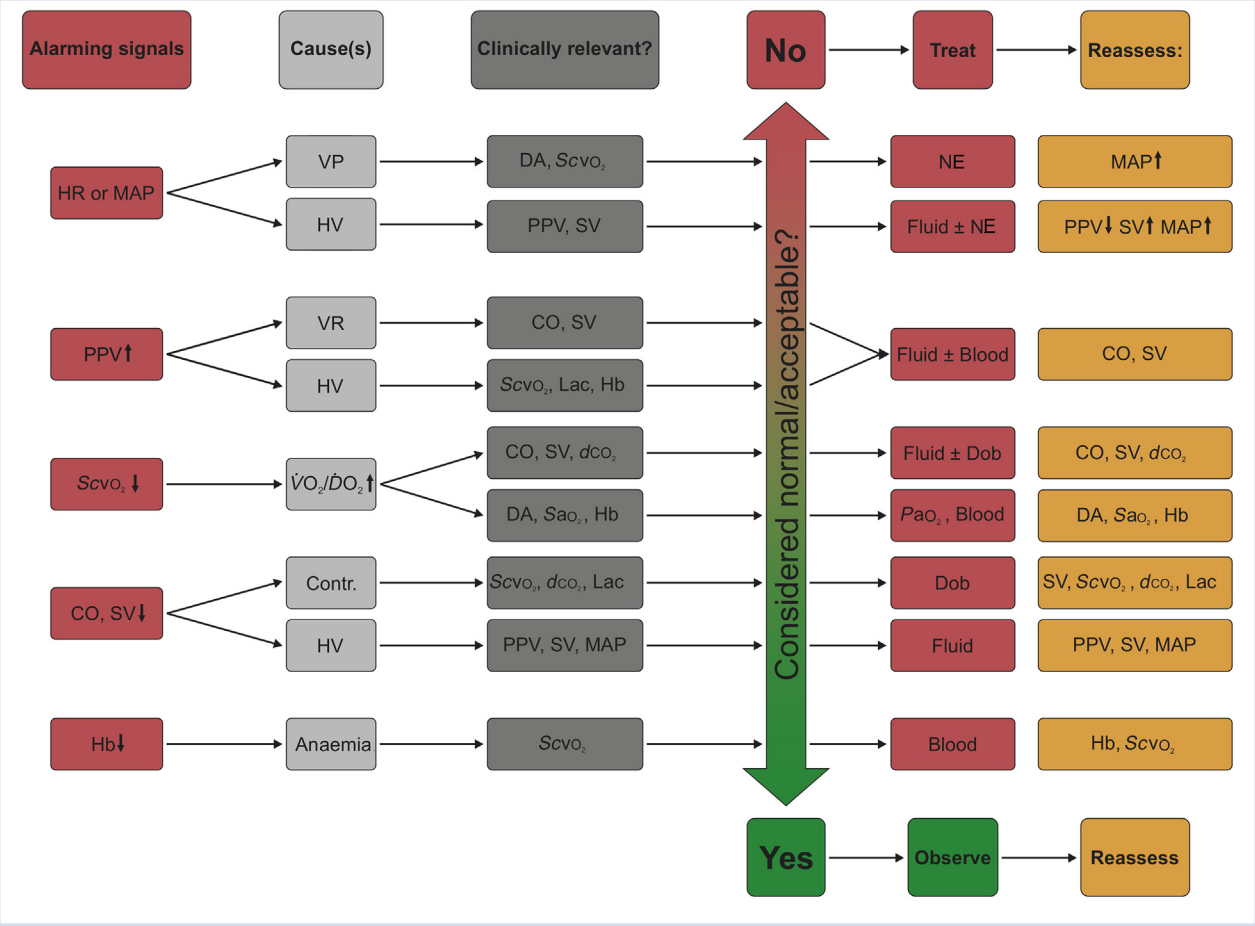

Fig 1. Multimodal, individualised, contextualised management of intraoperative cardiovascular dynamics. Whenever an *alarming signal* occurs, all potential *causes* should be considered to determine whether the alarming findings represent *clinically relevant* pathophysiology. This should be put in the context of detailed evaluation of measures of several indices reflecting cardiovascular dynamics, tissue perfusion, and the $\dot{V}o_2/\dot{D}o_2$ relationship. If considered clinically relevant, interventions to *treat* should be performed followed by frequent reassessment (*reassess*). If the *alarming signal* is regarded as false alarm, then *observe* and *reassess* later. CO, cardiac output; Contr, contractility; DA, depth of anaesthesia (bispectral index, MAC, etc.); dco_2, venous-to-arterial Pco_2 gap; Dob, dobutamine (representing positive inotropes); Hb, haemoglobin; HV, hypovolaemia; Lac, lactate; NE, norepinephrine (representing vasopressors); PPV, pulse pressure variation; $Scvo_2$, central venous oxygen saturation; SV, stroke volume; $\dot{V}o_2/\dot{D}o_2$, oxygen consumption/oxygen delivery; VP, vasoplegia; VR, volume responsiveness. ±, with or without.

propose a multimodal, individualised, contextualised approach to monitor and optimise cardiovascular dynamics and tissue perfusion in high-risk patients having major surgery.[8,9]

Changes in cardiovascular dynamics during surgery with general anaesthesia are complex and include impaired myocardial contractility, relative or absolute intravascular hypovolaemia, bradycardia, and thus eventually impaired blood flow (i.e. cardiac output). Arterial pressure is not the sole determinant of organ perfusion pressure and, although coupled to blood flow, is not a surrogate of blood flow or tissue perfusion. In some organ systems, especially brain and kidney, autoregulation enables blood flow to be kept constant (or adequate for actual needs) over a wide range of arterial pressure.[6,10] Only outside this autoregulatory range is organ perfusion pressure dependent. Blood flow autoregulation is governed by neuroregulatory systems and autoregulation thresholds that not only differ between individuals, but also between different organs.[10] Therefore, intraoperative hypotension should not be perceived as a specific entity, but as one of many signs reflecting profound alterations in cardiovascular dynamics. Conversely, normotension does not guarantee adequate organ blood flow and may just mimic an underlying redistribution of flow from 'less important' organs (gastrointestinal tract and kidney) towards the so-called vital organs (i.e. brain and heart). This 'occult hypoperfusion' can make such organs prone to dysfunction, infection, or disturbances in healing.[11] Tissue perfusion and oxygenation are regulated and influenced by various cardiovascular variables in addition to arterial pressure, including arterial oxygen content and cardiac output. Optimisation of these global haemodynamic variables led to improvement of tissue perfusion and tissue oxygen tension in several studies.[4,12]

Systematic optimisation of cardiovascular dynamics and tissue oxygenation therefore requires multimodal perioperative goal-directed therapy; this is not the same as protocolised

haemodynamic treatment of early sepsis (i.e. early goal-directed therapy). The proactive nature of perioperative goal-directed therapy (i.e. haemodynamics are pre-emptively modulated before or during the surgical trauma in contrast to the re-active nature of sepsis or trauma treatments) is probably the most important difference.[13] Perioperative goal-directed therapy is based on the concept of advanced haemodynamic monitoring; to be most effective, it should combine indicators of preload and fluid responsiveness with blood flow variables (including cardiac output and derivatives).[14,15] Perioperative goal-directed therapy improves the macrocirculation, which should result in improved oxygen delivery ($\dot{D}o_2$) and tissue perfusion.[4] Especially in high-risk patients and in those having major abdominal or soft tissue surgery, perioperative goal-directed therapy is associated with improved organ perfusion or function and less infection,[16,17] and in high-risk patients may even decrease mortality.[14] Based on this evidence, perioperative goal-directed therapy is considered part of care for high-risk surgical patients, but despite several positive studies is not well implemented in routine care.

One of the potential problems with perioperative goal-directed therapy algorithms using fixed target values of one single variable or a combination of variables is that they do not take into account individualised needs.[18] To ensure that haemodynamic variables are adequate for a given patient at a given moment during surgery, perioperative goal-directed therapy needs to be contextualised and individualised by repeatedly considering $\dot{D}o_2$, oxygen consumption ($\dot{V}o_2$), and tissue perfusion. There are several easily obtainable variables that can help provide a fuller clinical picture in addition to arterial pressure and blood flow variables (Fig. 1).

Mixed venous oxygen saturation (Svo_2) and its surrogate central venous oxygen saturation ($Scvo_2$) are the most commonly used methods to assess global oxygen extraction ($\dot{V}o_2/\dot{D}o_2$). The main factors influencing $Scvo_2$ are haemoglobin concentration, arterial oxygen saturation of haemoglobin, cardiac output, and $\dot{V}o_2$. Theoretically, if three of these factors are kept constant, the value of $Scvo_2$ reflects the changes of the other.[19]

Lactate, the end product of anaerobic metabolism, also has good prognostic value in high-risk surgical patients.[11] This makes serum lactate a useful tool to detect anaerobic metabolism and impaired tissue perfusion early, and to monitor the efficacy of resuscitation.

Another easily obtainable blood flow-related variable is central venous-to-arterial carbon dioxide gap (Pco_2 gap), which requires the parallel measurement of arterial and central venous blood carbon dioxide (CO_2). Adapting the Fick principle to CO_2 production and elimination, the following equation describes Pco_2 gap (where Vco_2 is CO_2 production and CO is cardiac output):[20]

$$P(v-a)CO_2 = \frac{Vco_2}{CO}$$

This clearly shows the indirect relationship between Pco_2 gap (normal value: 0.5–0.8 kPa) and cardiac output, and explains why an increased Pco_2 gap usually corresponds to low flow states. Its clinical relevance is further supported by its predictive value for worse outcome: high-risk surgical patients admitted to ICU with high Pco_2 gap developed more complications.[21] Additional prognostic information is given by combining $Scvo_2$ and Pco_2 gap.[22]

Guiding perioperative goal-directed therapy based on regional microcirculatory perfusion and tissue oxygenation would be an intriguing strategy. Unfortunately, the problem of how to assess regional microcirculatory perfusion and tissue oxygenation directly at the bedside is yet to be solved. Methods, such as laser Doppler and *in vivo* microscopy, have been tested, but only reflect regional microcirculatory perfusion and measurements are cumbersome, time consuming, not fully automated, and require skilled personnel.[23] Capillary refill time may be a simple and useful alternative to assess the microcirculation.

All of the aforementioned variables, besides arterial pressure, can indicate alterations in perioperative cardiovascular dynamics and serve as measures of treatment efficacy. Given the complex interaction and interdependency between these variables, getting the full picture is challenging, but mandatory. Treatment requirements vary widely amongst different patients and change over time in the same patient. In a prospective randomised trial comparing the effects of colloids and crystalloids during free-flap surgery, a multimodal approach was applied to patients in both groups.[24] Interestingly, during the whole surgery, some patients required only 0.5 L of fluids, but others needed almost 5 L to treat hypovolaemia, although the length of surgery (mean: 6 h) and blood loss were more or less similar in these patients. Applying individualised perioperative goal-directed therapy also helps identifying patients who benefit from positive inotropic support.[25] The marked inter-individual variability in fluid, vasopressor, and inotrope requirements emphasises the need for multimodal, individualised, contextualised perioperative goal-directed therapy based on advanced haemodynamic monitoring.

In conclusion, adverse postoperative outcomes are still common after major surgery. Therefore, we need to tackle this problem and avoid modifiable risk factors, such as intraoperative alterations in cardiovascular dynamics. Intraoperative hypotension has received a lot of attention recently, but may be just one of many signs reflecting profound alterations in cardiovascular dynamics. Alterations in cardiovascular dynamics are complex and include impaired myocardial contractility, relative or absolute intravascular hypovolaemia, bradycardia, and impaired regional blood flow. To monitor and optimise intraoperative cardiovascular dynamics and tissue perfusion in high-risk patients having major surgery, we propose multimodal, individualised, contextualised management approaches.

Authors' contributions

Drafting of paper: all authors
Creation of figure: all authors
Approval of final paper: all authors

Declarations of interest

ZM receives regular honoraria for being in the medical advisory board of Pulsion Medical Systems SE (Feldkirchen,

Germany), and for lectures from Biotest AG (Dreieich, Germany) and Thermo Fisher Scientific (Berlin, Germany). He also acts as a Medical Director for CytoSorbents Europe GmbH (Berlin, Germany). JB collaborates with Edwards Lifesciences Inc. (Irvine, CA, USA), CNSystems Medizintechnik GmbH (Graz, Austria), and Pulsion Medical Systems SE. BS has received honoraria for consulting, honoraria for giving lectures, and refunds of travel expenses from Edwards Lifesciences Inc. BS has received honoraria for consulting, institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems SE. BS has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH. BS has received institutional restricted research grants from Retia Medical LLC. (Valhalla, NY, USA). BS has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany). BS has received honoraria for consulting, institutional restricted research grants, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA).

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Another nail in the coffin of succinylcholine?

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Keywords: complications; neuromuscular blocking drugs; pharmacology; pulmonary; succinylcholine

In the 21st century, there has been little research published on the only available depolarising neuromuscular blocking drug, succinylcholine. The muscarinic side-effects of succinylcholine are well recognised,[1] as are its nicotinic effects such as postoperative myalgia,[2] an increase in intragastric,[3] intracranial[4] and intraocular pressure,[5] and hyperkalaemia.[6] Succinylcholine probably has the highest risk of anaphylaxis of any neuromuscular blocking drug.[7] Less frequent is the risk of a prolonged duration of action from either inherited or acquired causes.[1] This side-effect profile has caused neuromuscular pharmacologists to suggest that succinylcholine would not be approved by any medicines regulatory agency if it were being investigated as a new drug today.[8] In addition, the pharmacodynamic profile of succinylcholine is now considered to be less exceptional. The onset of action of sufficiently high doses of rocuronium (0.9–1.2 mg kg^{-1}) is fast enough to provide similar intubating conditions for rapid sequence induction and tracheal intubation to succinylcholine,[9] although succinylcholine does have less variability of effect.[10] The fast recovery from neuromuscular block induced by any neuromuscular blocking drug is not yet proven to be important in the management of a 'cannot ventilate, cannot intubate' scenario.[11] Nevertheless, sugammadex in appropriate dosage has the ability to provide rapid return of spontaneous ventilation by reversal of even high doses of rocuronium with as rapid a recovery as the ultrashort duration of action of succinylcholine,[12] assuming sugammadex is available and ready to use.[13] Interestingly, some European anaesthesia departments report that succinylcholine is rarely taken out of their emergency trolleys,[14] and is almost never administered.

In complete contrast, Schäfer and colleagues report in the *British Journal of Anaesthesia* a surprisingly high frequency of succinylcholine use in two distinguished university hospitals in the USA over a 12 year period between 2006 and 2017.[15] This latest contribution from the "Eikermann team", recognised for their thorough analysis of hospital registries, found that 14.2% of surgical patients had been treated with succinylcholine as the only neuromuscular blocking drug.[15] This rate is more than six-fold higher than the 2.3% observed in the European POPULAR study in 2014 and 2015.[16] Another 23.8% of the patients were treated with a combination of succinylcholine and a non-depolarising neuromuscular blocking drug, resulting in 38.0% of anaesthetised patients receiving at least one dose of succinylcholine. Three findings from this report must be emphasised. First, nearly every second patient (45.3%) who received a neuromuscular blocking drug received succinylcholine. Second, every fourth patient was exposed to a partial agonist at the nicotinic receptor (i.e. succinylcholine) and an antagonist, and a cholinesterase inhibitor with potentially unpredictable drug interactions. Thirdly, and most surprisingly, 1.5% of the patients received more than succinylcholine 2 mg kg^{-1}, and 0.5% of patients were treated with a succinylcholine infusion at a median dose of 3.9 mg kg^{-1}. This final point is particularly concerning, although we acknowledge that these are retrospective findings and practice may have changed in the subsequent few years.

This frequent use of succinylcholine allowed Schäfer and colleagues[15] to address one of the hottest topics in the field of

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