Best Practice & Research Clinical Anaesthesiology 33 (2019) 179–187

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

5

Perioperative goal-directed therapy – What is the evidence?

Thomas Kaufmann, MD, Research fellow, Anesthesiology [a], Bernd Saugel, MD, Professor, Consultant, Anesthesiology [b], Thomas W.L. Scheeren, MD, Professor, Consultant, Anesthesiology [a, *]

[a] *Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, P.O. Box 30.001, 9700 RB, Groningen, the Netherlands*
[b] *Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany*

Keywords:
hemodynamic monitoring
cardiovascular dynamics
cardiac output
pulse pressure variation
stroke volume variation

Perioperative goal-directed therapy aims at optimizing global hemodynamics during the perioperative period by titrating fluids, vasopressors, and/or inotropes to predefined hemodynamic goals. There is evidence on the benefit of perioperative goal-directed therapy, but its adoption into clinical practice is slow and incomprehensive. Current evidence indicates that treating patients according to perioperative goal-directed therapy protocols reduces morbidity and mortality, particularly in patients having high-risk surgery. Perioperative goal-directed therapy protocols need to be started early, should include vasoactive agents in addition to fluids, and should target blood flow related variables. Future promising developments in the field of perioperative goal-directed therapy include personalized hemodynamic management and closed-loop system management.

Introduction

Optimal hemodynamic management in patients undergoing surgery remains a challenge for anesthesiologists, and there is large variability in care between health care providers, even for the same

* Corresponding author.
E-mail addresses: t.kaufmann@umcg.nl (T. Kaufmann), b.saugel@uke.de (B. Saugel), t.w.l.scheeren@umcg.nl (T.W.L. Scheeren).

https://doi.org/10.1016/j.bpa.2019.05.005
1521-6896/

type of surgery and within the same hospital [1,2]. Insufficient hemodynamic management may lead to tissue hypoperfusion or tissue edema formation, both resulting in inadequate oxygen delivery to the tissue associated with organ dysfunction and adverse postoperative patient outcome [3]. To reduce the uncertainties regarding the optimal hemodynamic management, various protocols for perioperative goal-directed therapy (PGDT) have been proposed [4]. PGDT aims at optimizing global hemodynamics during the perioperative period by titrating fluids, vasopressors, and/or inotropes to predefined hemodynamic goals [5].

Since the first concepts of PGDT were described in the 1980s, more than 100 randomized controlled trials (RCTs) have been published, followed by an ever-increasing number of systematic reviews with meta-analyses. The cumulative evidence that PGDT is capable of improving patient outcome has led to its adoption in clinical practice guidelines, e.g., in the United Kingdom [6], France [7], and by the European Society of Anaesthesiology [8]. Despite this, the actual implementation and adoption of PGDT protocols in clinical practice has been rather slow and incomprehensive [9]. One reason for the poor adoption rate might be that PGDT is a vague, poorly defined, and confusing term for physicians and researchers, as it is used in multiple different clinical scenarios. In general, PGDT can involve optimization of cardiac preload, afterload, and contractility to achieve a balance between systematic oxygen delivery and oxygen demand.

In this review, we summarize the currently available evidence for PGDT. We discuss early trials employing a protocol guided by hemodynamic variables assessed with the pulmonary artery catheter (PAC) as well as trials using modern PGDT protocols with less invasive monitoring. In addition, we also critically discuss why studies on PGDT may have led to conflicting results. Finally, we consider future directions of PGDT, which may help to further evolve this research field.

Different concepts of perioperative goal-directed therapy

Early concepts of perioperative goal-directed therapy

The invention of the flow-directed balloon-tipped PAC in the 1970s has led to an increase in the use of invasive hemodynamic monitoring in critically ill patients [10]. However, it took some time for the first prospective RCT to be performed, which analyzed improvement of clinical outcome when using interventions guided by hemodynamic variables assessed with the PAC.

One of the first RCTs evaluated elderly patients undergoing hip fracture surgery, with the intervention group undergoing perioperative optimization of their hemodynamic status guided by PAC-derived variables [11]. In these patients, certain hemodynamic variables were monitored and optimized both pre- and postoperatively (among others, a cardiac index (CI) between 3.0 L min^{-1} m^{-2} and 3.5 L min^{-1} m^{-2} and oxygen consumption (VO_2) between 110 mL min^{-1} $m^{-2}$and 165 mL min^{-1} m^{-2}) [11]. This was one of the first treatment protocols that can be called PGDT. Patients treated according to this PAC-based protocol showed markedly lower postoperative mortality rates than control patients (1 of 35 (2.9%) versus 10 of 35 (29%)). Another RCT studied patients having surgery for peripheral vascular disease, who are at high risk of cardiovascular complications [12]. A preoperative optimization protocol was used targeting a pulmonary artery wedge pressure between 8 and 15 mmHg, a CI of more than 2.8 L min^{-1} m^{-2}, and a systemic vascular resistance of less than 1100 dyne-sec cm^{-5} [12]. Fluids, inotropes, and vasodilators could be used to achieve these goals, and in intervention group patients, the postoperative mortality was 1 of 68 (1.5%) compared to 1 of 21 (9.5%) in control group patients [12].

Supranormal oxygen delivery

Measurements of hemodynamic variables in survivors and nonsurvivors of shock after major trauma surgery suggested that higher – so-called supranormal – values of hemodynamic variables were associated with improved survival in these patients [13]. It was hypothesized that the survival benefit might be the consequence of less shock-related complications and organ failure in patients having supranormal values, e.g., CI of more than 4.5 L min^{-1} m^{-2}, oxygen delivery (DO_2) of more than 600 mL min^{-1} m^{-2}, and VO_2 of more than 170 mL min^{-1} m^{-2}. These values, which are higher than

normal resting hemodynamic values, were then used in prospective trials as target values for high-risk patients having major noncardiac surgery. The results of the first trial in high-risk patients showed a reduction in mortality, postoperative complications, and length of hospital stay after using a treatment protocol based on the supranormal target values [14]. These results led to the hypothesis that high-risk patients having surgery should be hemodynamically optimized to these targets already before surgery, i.e., before the surgical trauma and the development of organ failure. In addition, it was suggested to maintain these target values throughout surgery and also for the first 24 h after surgery in the ICU. Several trials used similar protocols with varying results [11,15–21]. These early trials were summarized in a systematic review with meta-analysis by the original author of the first trial, who concluded that preoperative initiation of the protocol was associated with a decrease in mortality [22]. It was emphasized that PGDT protocols have to be initiated early and aggressively to be most effective [22].

Investigators in these initial studies on PGDT used the PAC to monitor patient hemodynamics and guide interventions [10]. Consequently, the use of the PAC became widespread and the PAC-derived hemodynamic data were used by physicians to guide hemodynamic therapy in the ICU and the operating room. At its peak, more than 40% of all critically ill patients received a PAC as part of their care in the ICU, but evidence regarding its benefit was never objectified [23]. The invasiveness of the PAC also meant that placement was associated with complications such as catheter-related infections and thromboembolic events. In one of the largest trials comparing a PGDT protocol based on PAC-derived hemodynamic variables with standard care without the use of a PAC, no survival benefit was found for PAC-guided therapy in high-risk surgical patients [24]. The results of this RCT and numerous other trials combined in a Cochrane review led to a decrease in the use of the PAC [25,26]. Also, routine PAC placement is not recommended by the European Society of Cardiology/European Society of Anaesthesiology in their current guidelines on the management of patients undergoing noncardiac surgery [27]. In addition, optimizing patients preoperatively with a PAC requires admission to an ICU, which consumes many resources and is therefore not applicable to patients undergoing most types of surgery. The decline of the use of the PAC was further facilitated by the emergence of minimally invasive and noninvasive monitoring techniques to estimate cardiac output (CO) and other hemodynamic variables.

Minimally invasive and noninvasive monitoring in PGDT protocols

Minimally invasive monitoring refers to devices that measure hemodynamic variables by only using an arterial catheter or esophageal Doppler [28]. Several of these devices have been developed, and the most important ones are discussed here.

Pulse wave analysis

Pulse wave analysis (PWA) allows estimation of SV/CO and of dynamic preload variables. The method is based on the principle that aortic pulse pressure is proportional to stroke volume (SV) and inversely proportional to aortic compliance. Although static variables are single snapshots taken at specific points in the cardiac cycle (e.g., CO measured by thermodilution or central venous pressure (CVP)), dynamic preload variables express rapid changes in the cardiovascular status and can be monitored continuously. In addition, an increase in CO induced by volume expansion can be predicted by dynamic preload variables before volume expansion is actually performed, which is helpful in PGDT algorithms and helps to avoid unnecessary fluid administration.

Examples of these dynamic preload variables include systolic pressure variation (SPV), pulse pressure variation (PPV), and stroke volume variation (SVV). These variables are induced by heart–lung interactions during a respiratory cycle in mechanically ventilated patients and are an indicator of the position on the Frank–Starling curve, which is proportional to the degree of preload dependency [29,30]. Of these dynamic variables, PPV is considered to have the best predictive ability for fluid responsiveness [31]. A disadvantage of these dynamic preload variables is that they cannot be used in a number of concomitant conditions including cardiac arrhythmias and spontaneous breathing [32].

Some PWA monitors can be calibrated with an independent measurement of CO done by transpulmonary thermodilution. This calibration is done similar to the PAC with injection of a small fluid bolus. To do this, transpulmonary thermodilution monitors require both a central venous catheter and

a femoral arterial catheter and are therefore considered invasive, not minimally invasive [28]. Transpulmonary thermodilution monitors can also estimate extravascular lung water, which is a measure of pulmonary edema, and pulmonary vascular permeability, which is a measure of pulmonary capillary leakage. These variables can help to guide fluid strategies, for example, as safety measures to avoid fluid overload in patients with acute respiratory distress syndrome. Transpulmonary thermodilution monitors are therefore mainly used for complex patients in the ICU [33].

Uncalibrated PWA monitors estimate the CO only from arterial pressure waveform characteristics and biometric data. A proprietary algorithm uses the mean, standard deviation, skewness, and kurtosis of arterial pressure and arterial compliance estimated from sex, age, weight, and height [34]. The waveform characteristics become less reliable in pathophysiological conditions with low vascular resistance such as liver disease, during liver surgery, or septic shock. In these conditions, use of uncalibrated PWA monitors is not recommended [35].

Oesophageal Doppler Monitor

The Oesophageal Doppler Monitor (ODM) probe is placed in the patient's oesophagus and uses Doppler ultrasound to measure the velocity of blood flow in the adjacent descending aorta. The blood flow in the descending aorta is correlated to CO, assuming a fixed proportion of blood flow going to the upper and lower part of the body. Estimation of CO using the ODM was originally thought to have agreement with invasive CO measurements using the PAC [36]. However, results of a more recent systematic review with meta-analysis have shown that agreement between ODM and PAC derived CO measurements is moderate at best [37].

Several PGDT protocols using ODM-derived hemodynamic variables have been developed and tested. The first trials evaluated a PGDT protocol using an ODM to titrate fluids in patients undergoing hip fracture surgery [38,39]. Both studies concluded that intraoperative volume loading to optimize stroke volume using an ODM resulted in more rapid postoperative recovery and a reduced length of hospital stay. Use of ODM was not limited to hip fracture surgery patients but ODM was also used to titrate fluids and vasoactive medication in patients undergoing abdominal surgery [40]. This was also associated with a reduction in length of hospital stay, but also in postoperative complications, number of patients requiring ICU admission, and time to return of bowel function [40]. Eventually, use of PGDT protocols employing an ODM was implemented in national guidelines in the United Kingdom to enhance recovery after surgery [6]. In general, a limitation of the ODM is that it can only be placed intraoperatively under general anesthesia due to patient convenience.

Perioperative goal-directed therapy – what is the evidence?

Summarizing the evidence on PGDT is challenging because many different protocols have been developed and studied over the years. Nevertheless, a multitude of meta-analyses has been conducted on this subject. Several meta-analyses have suggested a beneficial effect of PGDT in terms of reduction in postoperative complications and length of stay [41–43]. However, the studies included in these meta-analyses were heterogeneous and varied with regard to not only types of surgery but also all individual components of the PGDT intervention, including the timing of the intervention; the type of monitoring device; the hemodynamic variables assessed; the hemodynamic values targeted; and the types and amounts of fluids, vasopressors, and/or inotropes used [44]. This clinical heterogeneity needs to be considered when pooling results of individual RCTs [45].

We previously performed a systematic review on PGDT where the observed clinical heterogeneity made us conclude that it was inappropriate to pool all the data to estimate an intervention effect of the PGDT intervention [44]. Therefore, we believe a definite conclusion on the effect of PGDT remains to be elucidated [44].

Recently, a systematic review with meta-analysis was published with more rigorous methodological conditions [4]. Benefit for PGDT was analyzed in various predefined subgroups, such as timing of initiation of PGDT protocol or whether a CO monitoring device was used. Subgroup analysis can be a way of reducing clinical heterogeneity within a meta-analysis, particularly if different patient populations, technologies, and interventions exist within the literature. This approach also takes into

account that many aspects of the management of high-risk surgical patients and trial methodology may have changed over the last decades [46]. The authors of this systematic review discuss a number of results. First, PGDT reduced the risk of mortality compared with standard care only in high-risk patients (OR 0.60 (95% CI 0.42–0.85)) but not in low-risk patients (OR 0.79 (95% CI 0.50–1.24)) [4]. High risk was defined as patients undergoing cardiac surgery, critically ill patients, or studies with >50% ASA III physical class patients. Second, PGDT reduced the risk of mortality compared with standard care only if PGDT was started intraoperatively (OR 0.65 (95% CI 0.47–0.89)) and not when PGDT was started postoperatively (OR 0.72 (95% CI 0.38–1.33)) [4]. Third, PGDT reduced mortality only if vasoactive agents were used per protocol in addition to fluids (OR 0.59 (95% CI 0.40–0.89)) and not if only a fluid-based intervention was performed (OR 0.65 (95% CI 0.41–1.05)) [4]. Last, PGDT reduced mortality only if a CO monitor was used to guide therapy (OR 0.68 (95% CI 0.49–0.95)) [4].

Based on the abovementioned evidence, we believe that PGDT should be employed in patients who will benefit the most: high-risk patients undergoing high-risk surgery. The PGDT protocol should be started early during the perioperative period [47]. In addition, an algorithm which mainly targets flow optimization (i.e., CO or SV) should be used, and dynamic preload variables might also be included to assess fluid responsiveness.

Two large RCTs on PGDT are currently being conducted. The first is the FLuid Optimisation in Emergency LAparotomy (FLO-ELA) trial (www.floela.org), which aims to include 7646 patients undergoing emergency bowel surgery using a PGDT protocol. The other trial is the OPtimisation of Peri-operaTive CardIovascular Management to Improve Surgical outcomE II (OPTIMISE II) trial (www.optimiseii.org), which aims to include 2502 patients undergoing elective major abdominal surgery. Currently, a third large multicenter trial is being analyzed, and results should soon be available [48].

Perioperative goal-directed therapy – future directions

Personalized hemodynamic management

The above-mentioned methods and PGDT protocols all use a general strategy of hemodynamic optimization employing predefined “normal” values as hemodynamic targets. However, it is now known that many hemodynamic variables have marked inter-individual variability and depend on biometric factors [49]. For example, CO measured by transpulmonary thermodilution in critically ill patients was shown to be independently associated with age, height, and body weight [50]. In addition, left ventricular volume and stroke volume varies by gender and decreases with age [51,52]. Consequently, the term personalized hemodynamic management has been suggested as a means to optimize cardiovascular dynamics based on the patient's personal hemodynamic profile [49]. For PGDT, this could be realized by implementing personalized concepts of hemodynamic management based on individual baseline values and functional assessment of fluid responsiveness in the operating room.

Closed-loop system management

Other developments such as closed-loop system management are suggested to further help implementing PGDT protocols in clinical practice. One of the largest trials on PGDT showed that there is a learning curve for clinicians and that compliance to PGDT protocols is suboptimal [53]. A possible way of integrating the monitoring of the variables in one place and increasing the compliance to the protocols is by implementing a closed-loop system for hemodynamic management. A closed-loop system is a system where a controller monitors multiple variables and adjusts interventions using a feedback process [54]. In the context of PGDT, a clinical example of a closed-loop system uses dynamic variables (e.g., PPV and SVV) collected from an uncalibrated PCA monitor to automatically titrate fluid application. This system has been tested in simulation [55,56], engineering studies [57], and animal studies [58]. Clinical studies in patients undergoing moderate- and high-risk surgery have established feasibility of implementing these systems and show that patients consequently spent a great portion of time in a preload-independent state throughout surgery [59,60]. At the moment, the feasibility of a

closed-loop system for vasopressor infusion is being developed, with initial promising results in simulation and animal studies [61,62].

Summary

Perioperative goal-directed therapy aims at optimizing global hemodynamics during the perioperative period by titrating fluids, vasopressors, and/or inotropes to predefined hemodynamic goals. There is evidence on the benefit of perioperative goal-directed therapy, but its adoption into clinical practice is slow and incomprehensive. Current evidence indicates that treating patients according to perioperative goal-directed therapy protocols reduces morbidity and mortality, particularly in patients having high-risk surgery. Perioperative goal-directed therapy protocols need to be started early, should include vasoactive agents in addition to fluids, and should target blood flow related variables. Future promising developments in the field of perioperative goal-directed therapy include personalized hemodynamic management and closed-loop system management.

Practice points

- Current evidence indicates that treating patients according to PGDT protocols reduces morbidity and mortality, particularly in patients undergoing high-risk surgery. The PGDT protocol needs to be started early (i.e., intraoperatively, not postoperatively), should include vasoactive agents in addition to fluids, and should target blood flow related variables.
- Clinical heterogeneity between different studies makes drawing definite conclusions on the benefit of PGDT on outcome difficult so that multicenter trials on this topic are still needed.

Research agenda

- Large multicenter trials (OPTIMISE-II and FLO-ELA) are ongoing to further elucidate the benefit of PGDT protocols.
- Future PGDT protocols will consider individual variability in optimal hemodynamic targets and move toward personalized hemodynamic management.
- Further research on closed-loop systems to administer fluids and vasoactive agents will help with improving protocol compliance.

Conflicts of interest

TK has no conflicts of interest.

BS has collaboration with Pulsion Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board and has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems SE. BS has received research support, honoraria for giving lectures, and honoraria for consulting from Edwards Lifesciences (Irvine, CA, USA). BS has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria). BS has received institutional restricted research grants, honoraria for consulting, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA). BS has also 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).

TWLS received research grants and honoraria from Edwards Lifesciences (Irvine, CA, USA) and Masimo Inc. (Irvine, CA, USA) for consulting and lecturing and from Pulsion Medical Systems SE (Feldkirchen, Germany) for lecturing.

Acknowledgments

None.

References

[1] Minto G, Mythen MG. Perioperative fluid management: science, art or random chaos? Br J Anaesth 2015;114:717–21. https://doi.org/10.1093/bja/aev067.
[2] Ehrenfeld JM, Cannesson M, Lilot M, et al. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. Br J Anaesth 2015;114:767–76. https://doi.org/10.1093/bja/aeu452.
*[3] Shin CH, Long DR, McLean D, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. Ann Surg 2018;267:1084–92. https://doi.org/10.1097/SLA.0000000000002220.
*[4] Chong MA, Wang Y, Berbenetz NM, et al. Does goal-directed haemodynamic and fluid therapy improve peri-operative outcomes? Eur J Anaesthesiol 2018;35:469–83. https://doi.org/10.1097/EJA.0000000000000778.
[5] Cove ME, Pinsky MR. Perioperative hemodynamic monitoring. Best Pract Res Clin Anaesthesiol 2012;26:453–62. https://doi.org/10.1016/j.bpa.2012.10.003.
[6] National Institute for Health and Clinical Excellence. Medical technologies guidance MTG3: CardioQ-ODM Oesophageal Doppler Monitor. 2011.
[7] Vallet B, Blanloeil Y, Cholley B, et al. Guidelines for perioperative haemodynamic optimization. Ann Fr Anesth Reanim 2013;32:e151–8. https://doi.org/10.1016/j.annfar.2013.09.010.
[8] European Society of Anaesthesiology - PerioPerative goal- Directed TheraPy protocol summary. http://html.esahq.org/patientsafetykit/resources/downloads/05_Checklists/Various_Checklists/Perioperative_Goal_Directed_Therapy_Protocols.pdf.
[9] Cannesson M, Pestel G, Ricks C, et al. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. Crit Care 2011;15:R197. https://doi.org/10.1186/cc10364.
[10] Swan HJ, Ganz W, Forrester J, et al. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 1970;283:447–51. https://doi.org/10.1056/NEJM197008272830902.
[11] Schultz RJ, Whitfield GF, LaMura JJ, et al. The role of physiologic monitoring in patients with fractures of the hip. J Trauma 1985;25:309–16.
[12] Berlauk JF, Abrams JH, Gilmour IJ, et al. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery. A prospective, randomized clinical trial. Ann Surg 1991;214:289–97. https://doi.org/10.1097/00000658-199109000-00011. discussion 298-9.
[13] Shoemaker WC, Montgomery ES, Kaplan E, et al. Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death. Arch Surg 1973;106:630–6.
*[14] Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988;94:1176–86. https://doi.org/10.1378/chest.94.6.1176.
[15] Fleming A, Bishop M, Shoemaker W, et al. Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 1992;127:1175–9. https://doi.org/10.1001/archsurg.1992.01420100033006. discussion 1179-81.
[16] Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. J Am Med Assoc 1993;270:2699–707. https://doi.org/10.1007/s00134-013-3098-2.
[17] Bishop MH, Shoemaker WC, Appel PL, et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma Inj Infect Crit Care 1995;38:780–7. https://doi.org/10.1097/00005373-199505000-00018.
[18] Ueno S, Tanabe G, Yamada H, et al. Response of patients with cirrhosis who have undergone partial hepatectomy to treatment aimed at achieving supranormal oxygen delivery and consumption. Surgery 1998;123:278–86. https://doi.org/10.1016/S0039-6060(98)70180-1.
[19] Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 1999;318:1099–103.
[20] Velmahos GC, Demetriades D, Shoemaker WC, et al. Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. Ann Surg 2000;232:409–18. https://doi.org/10.1007/BF03019819.
[21] Lobo SMA, Salgado PF, Castillo VGT, et al. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 2000;28:3396–404. https://doi.org/10.1097/00003246-200010000-00003.
[22] Kern JW, Shoemaker WC. Meta-analysis of hemodynamic optimization in high-risk patients. Crit Care Med 2002;30:1686–92. https://doi.org/10.1097/00003246-200208000-00002.
[23] Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill pateints. JAMA Res Libr Pg 1996:276. https://www.ncbi.nlm.nih.gov/pubmed/8782638.
*[24] Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348:5–14. https://doi.org/10.1056/NEJMoa021108＼348/1/5.

[25] Wiener RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993-2004. J Am Med Assoc 2007;298:1993–2004. https://doi.org/10.1001/jama.298.4.423.
[26] Rajaram SS, Desai NK, Kalra A, et al. Pulmonary artery catheters for adult patients in intensive care. Cochrane Database Syst Rev 2013;373:CD003408. https://doi.org/10.1002/14651858.CD003408.pub3.
[27] Kristensen SD, Knuuti J, Saraste A, et al. ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the joint task force on non-cardiac surgery: cardiovascular assessment and management of the european society of Cardiology (ESC) and the European society of anaesth. Eur Heart J 2014;35:2383–431. https://doi.org/10.1093/eurheartj/ehu282. 2014.
[28] Saugel B, Vincent J-L. Cardiac output monitoring: how to choose the optimal method for the individual patient. Curr Opin Crit Care 2018;24:165–72. https://doi.org/10.1097/MCC.0000000000000492.
[29] Reuter DA, Felbinger TW, Schmidt C, et al. Stroke volume variations for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. Intensive Care Med 2002;28:392–8. https://doi.org/10.1007/s00134-002-1211-z.
[30] Michard F. Changes in arterial pressure during mechanical ventilation. Anesthesiology 2005;103:419–28.
[31] Marik PE, Cavallazzi R, Vasu T, et al. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 2009;37:2642–7. https://doi.org/10.1097/CCM.0b013e3181a590da.
[32] Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. Ann Intensive Care 2016;6:1–11. https://doi.org/10.1186/s13613-016-0216-7.
[33] Monnet X, Teboul JL. Transpulmonary thermodilution: advantages and limits. Crit Care 2017;21:1–12. https://doi.org/10.1186/s13054-017-1739-5.
[34] Langewouters GJ, Wesseling KH, Goedhard WJ. The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. J Biomech 1985;18:613–20.
[35] Slagt C, Malagon I, Groeneveld ABJ. Systematic review of uncalibrated arterial pressure waveform analysis to determine cardiac output and stroke volume variation. Br J Anaesth 2014;112:626–37. https://doi.org/10.1093/bja/aet429.
[36] Singer M, Bennett ED. Noninvasive optimization of left ventricular filling using esophageal Doppler. Crit Care Med 1991;19:1132–7.
[37] Peyton PJ, Chong SW. Minimally invasive measurement of cardiac output during surgery and critical care. Anesthesiology 2010;113:1220–35. https://doi.org/10.1097/ALN.0b013e3181ee3130.
[38] Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 1997;315:909–12. https://doi.org/10.1136/bmj.315.7113.909.
[39] Venn R, Steele A, Richardson P, et al. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 2002;88:65–71. https://doi.org/10.1093/bja/88.1.65.
[40] Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 2008;63:44–51. https://doi.org/10.1111/j.1365-2044.2007.05233.x.
*[41] Benes J, Giglio M, Brienza N, et al. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. Crit Care 2014;18:1–11. https://doi.org/10.1186/s13054-014-0584-z.
[42] Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. Crit Care 2013;17:209. https://doi.org/10.1186/cc11823.
*[43] Michard F, Giglio MT, Brienza N. Perioperative goal-directed therapy with uncalibrated pulse contour methods: impact on fluid management and postoperative outcome. Br J Anaesth 2017;119:22–30. https://doi.org/10.1093/bja/aex138.
*[44] Kaufmann T, Clement RP, Scheeren TWL, et al. Perioperative goal-directed therapy: a systematic review without meta-analysis. Acta Anaesthesiol Scand 2018;62:1340–55. https://doi.org/10.1111/aas.13212.
[45] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011. Version 5.1.0 (updated March 2011), 2011.
[46] Gillies MA, Pearse R, Chew MS. Peri-operative goal-directed therapy. Eur J Anaesthesiol 2018;35:467–8. https://doi.org/10.1097/EJA.0000000000000812.
[47] Saugel B, Michard F, Scheeren TWL. Goal-directed therapy: hit early and personalize! J Clin Monit Comput 2018;32:375–7. https://doi.org/10.1007/s10877-017-0043-x.
[48] Montenij L, de Waal E, Frank M, et al. Influence of early goal-directed therapy using arterial waveform analysis on major complications after high-risk abdominal surgery: study protocol for a multicenter randomized controlled superiority trial. Trials 2014;15:360. https://doi.org/10.1186/1745-6215-15-360.
*[49] Saugel B, Vincent JL, Wagner JY. Personalized hemodynamic management. Curr Opin Crit Care 2017;23:334–41. https://doi.org/10.1097/MCC.0000000000000422.
[50] Saugel B, Mair S, Götz SQ, et al. Indexation of cardiac output to biometric parameters in critically ill patients: a systematic analysis of a transpulmonary thermodilution-derived database. J Crit Care 2015;30:957–62. https://doi.org/10.1016/j.jcrc.2015.06.011.
[51] Cain PA, Ahl R, Hedstrom E, et al. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study. BMC Med Imaging 2009;9. https://doi.org/10.1186/1471-2342-9-2.
[52] Kou S, Caballero L, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. Eur Heart J Cardiovasc Imaging 2014;15:680–90. https://doi.org/10.1093/ehjci/jet284.
*[53] Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. J Am Med Assoc 2014;311:2181–90. https://doi.org/10.1001/jama.2014.5305.
[54] Rinehart J, Liu N, Alexander B, et al. Review article: closed-loop systems in anesthesia: is there a potential for closed-loop fluid management and hemodynamic optimization? Anesth Analg 2012;114:130–43. https://doi.org/10.1213/ANE.0b013e318230e9e0.

[55] Rinehart J, Alexander B, Le Manach Y, et al. Evaluation of a novel closed-loop fluid-administration system based on dynamic predictors of fluid responsiveness: an in silico simulation study. Crit Care 2011;15:R278. https://doi.org/10.1186/cc10562.
[56] Rinehart J, Chung E, Canales C, et al. Intraoperative stroke volume optimization using stroke volume, arterial pressure, and heart rate: closed-loop (learning intravenous resuscitator) versus anesthesiologists. J Cardiothorac Vasc Anesth 2012;26:933–9. https://doi.org/10.1053/j.jvca.2012.05.015.
[57] Rinehart J, Lee C, Cannesson M, et al. Closed-loop fluid resuscitation. Anesth Analg 2013;117:1110–8. https://doi.org/10.1213/ANE.0b013e3182930050.
[58] Rinehart J, Lee C, Canales C, et al. Closed-loop fluid administration compared to anesthesiologist management for hemodynamic optimization and resuscitation during surgery. Anesth Analg 2013;117:1119–29. https://doi.org/10.1213/ANE.0b013e3182937d61.
*[59] Joosten A, Huynh T, Suehiro K, et al. Goal-Directed fluid therapy with closed-loop assistance during moderate risk surgery using noninvasive cardiac output monitoring: a pilot study. Br J Anaesth 2015;114:886–92. https://doi.org/10.1093/bja/aev002.
[60] Rinehart J, Lilot M, Lee C, et al. Closed-loop assisted versus manual goal-directed fluid therapy during high-risk abdominal surgery: a case-control study with propensity matching. Crit Care 2015;19:1–11. https://doi.org/10.1186/s13054-015-0827-7.
[61] Rinehart J, Joosten A, Ma M, et al. Closed-loop vasopressor control: in-silico study of robustness against pharmacodynamic variability. J Clin Monit Comput 2018. https://doi.org/10.1007/s10877-018-0234-0.
[62] Joosten A, Delaporte A, Alexander B, et al. Automated titration of vasopressor infusion using a closed-loop controller: in vivo feasibility study using a swine model. Anesthesiology 2019;130:394–403. https://doi.org/10.1097/ALN.0000000000002581.