Perioperative Goal-Directed Hemodynamic Therapy: From Invasive Monitoring To Automated Physiological Closed-Loop Systems

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Abstract

Perioperative goal-directed hemodynamic therapy (GDHT) has evolved from invasive "supra-physiological" maximization of oxygen delivery into minimally and non-invasively guided automated stroke volume optimization. Throughout this evolution, investigators have simultaneously developed novel monitors, updated strategies, and automated technologies to aid them in GDHT implementation. In particular, closed-loop systems have been created to both increase GDHT compliance and decrease physician workload. Currently, these automated systems offer an elegant approach to help the clinician optimize cardiac output and end-organ perfusion during the perioperative period. Most notably, automated fluid optimization guided by dynamic parameters of fluid responsiveness has shown its feasibility, safety, and impact. Making the leap into fully automated GDHT has been accomplished on a small scale, but there are considerable challenges that must be surpassed before integrating all hemodynamic components into an automated system during general anesthesia. In this review we will discuss the potential future of automated GDHT by covering the key events that paved the way from initially complex and time consuming approaches to simple yet effective hands-free strategies.

Background

Modern anesthesia revolutionized medicine and introduced countless technological advances that have greatly improved patient safety. Anesthesiologists are now both specialists in anesthesia delivery and experts in perioperative medicine. Nevertheless, morbidity and mortality still occur in surgical patients. Postoperative complications both negatively impact patient wellbeing and significantly increase healthcare costs [1]. In 2012, an observational study reported that perioperative mortality in Europe remained as high as 4%. The study also underlined the limitations of current perioperative medicine and the need for improved patient care [2]. High-risk patients, defined either by their age, comorbidities, or the surgery itself, make up 15% of the global surgical population and 80% of perioperative deaths [3]. The overwhelming cause of death in these patients is fundamentally due to cellular hypoxia following an inadequate balance between oxygen delivery (Do_2) and tissue metabolic demand (Vo_2) [4]. Goal-directed hemodynamic therapy (GDHT) is a strategy that aims to correct this imbalance and its associated complications. This strategy first appeared in the 1980s and remains a key topic in perioperative and intensive care medicine today. Over the last decade, automation of fluid delivery for left ventricular preload optimization has shown strong promise while a fully automated GDHT system may soon become a realistic approach for personalizing cardiac output (CO) and end organ perfusion.

From Maximizing Oxygen Delivery To Optimizing Stroke Volume

In 1985, Schultz et al. published a randomized controlled trial (RCT) that demonstrated the benefits of hemodynamic maximization in patients undergoing hip fracture repair [5]. A total of 70 patients were randomized to receive either standard care or preoperative, intraoperative, and postoperative GDHT guided invasively with a Swan-Ganz catheter. Mortality decreased tenfold from 29% in the standard care group to 2.9% in the GDHT group. The same year, another cohort study of 220 critically ill surgical patients determined that patients that survived had improved cardiac function, better pulmonary reserve, lower pulmonary artery pressure, increased Do_2, and increased Vo_2 despite both survivors and non-survivors initially having vital signs within the normal range. Non-survivors, on the other hand, developed lactic acidosis that was attributed to a defect in oxygen extraction due to microcirculatory alterations [6]. In 1988, Shoemaker et al. demonstrated the detrimental effect of perioperative tissue oxygen debt, defined as the measured Vo_2 minus the estimated Vo_2 requirements. All patients developed tissue oxygen debt during the intraoperative and immediate postoperative periods. While survivors quickly compensated tissue oxygen debt, it persisted and increased in non-survivors [7]. These studies led to the hypothesis that a hemodynamic approach that aimed at maximizing Do_2 would decrease perioperative mortality and morbidity related to tissue hypoxia.

Shoemaker et al. tested this hypothesis in a population of high-risk surgical patients in a RCT that compared standard care with or without invasive hemodynamic monitoring to a Swan-Ganz guided supra-physiological group having the following hemodynamic goals: CI > 4.5 L/min/m², Do_2> 600 ml/min and Vo_2 > 170 ml/min/m². Patients in the supra-physiological GDHT group had less postoperative complications, shorter intensive care unit (ICU) length of stay (LOS), and reduced mortality. In 1993, Boyd et al. confirmed this hypothesis in a RCT of 107 mostly surgical trauma patients [8]. They showed once again that maximizing patient Do_2 with a supra-physiological GDHT strategy in the preoperative, intraoperative, and postoperative periods led to decreased morbidity and mortality. In a follow-up study of these patients, the authors noted that long term survival was also greater in the supra-physiological GDHT group [9]. Shoemaker and his team would then attempt to determine, on the one hand, which patients would benefit the most from this strategy [10, 11] and on the other hand, the ideal time to start hemodynamic maximization [12].

Other teams, however, soon published conflicting results in studies using similar designs [13-16]. In their meta-analysis of 7 studies that included a total of 1016 patients, Heyland et al. reported that a GDHT strategy targeting supra-physiological CI, Do_2, and Vo_2 in critically ill patients was not associated with decreased mortality, with the possible exception of a preoperative approach [17]. These concerning results would be reaffirmed by Russel et al [18]. Despite these contradictory results, the search for an ideal perioperative hemodynamic strategy led several authors to conceive simpler GDHT strategies, such as the maximization of Do_2 by focusing predominantly on CO. In 1995, one of the initial studies aimed at stroke volume (SV) maximization through the use of transesophageal Doppler. Investigators randomized 60 cardiac surgery patients with preserved left ventricular function (FEVG>50%) to either receive standard care or 200 ml boluses of hydroxyethyl starch based colloid every 15 minutes until SV was maximized [19]. Their results confirmed that maximizing CO led to decreased postoperative complications and hospital LOS. Studying gastric mucosal perfusion with tonometric assessment of gastric intramucosal pH, the authors also showed improved splanchnic perfusion in the GDHT group. Two years later, Sinclair et al. demonstrated that in patients undergoing proximal femoral fracture repair, Doppler guided GDHT decreased postoperative complications and shortened LOS [20]. In addition, half of the patients that developed splanchnic hypoxia did not have noticeable blood pressure decrease, which reaffirms the limitation of blood pressure as a predictor of tissue oxygenation. In the years that followed, many RCTs demonstrated that, when compared to fluid management guided by static parameters such as central venous pressure and heart rate, a GDHT strategy leads to decreased postoperative complications, less postoperative ileus, and shorter length of stay in various surgical populations [21, 22].

From 1985 to 2000, surgeons, intensivists and anesthesiologists pioneered strategies based on "supra-physiological" maximization of hemodynamics to improve outcome in high risk patients [23]. Such strategies had their limitations, especially in patient unable to improve their hemodynamic status despite aggressive use of fluids, vasopressors, and inotropes [24, 25]. Maximizing SV, for example, could lead to complications associated with fluid overload [26]. A better approach has since been described that aims to limit fluid infusion so as to optimize, and not maximize, SV by using an approach that adapts to the patient's fluid responsiveness [27]. In the following years, anesthetist would simplify these strategies to focus mainly on CO optimization, while a concomitant paradigm shift would push fluid administration away from the arbitrary concept of "restrictive versus liberal fluid therapy" towards a "goal-directed" strategy.

Fluid Therapy: Breaking Away From The "restrictive Versus Liberal" Paradigm

Before Mythen et al.'s demonstration of the potential of SV optimization using colloids guided by transesophageal Doppler, [19] most anesthesiologist administered liberal amounts of fluid and based their strategy on static parameters such as blood pressure, heart rate, and central venous pressure. Arguments for a liberal approach included fluid loss from preoperative fasting, insensible losses, diuresis, hemorrhage, and third space redistribution. However, several of these phenomena, such as preoperative fasting, the amount of insensible fluid loss, and the "third space" have never been clearly demonstrated [28]. This realization and the increased evidence of the negative impact of excessive fluids [29, 30] progressively led towards a shift from liberal to restrictive fluid management.

At the start of the 21th century, numerous teams compared restrictive versus liberal fluid strategies [29, 30]. In a multicenter RCT of 172 patients, Brandstrup et al. found that a restrictive approach (i.e. volume-to-volume compensation with a colloid), when compared to what at that time was standard care (i.e. 3-7 ml/kg/h crystalloid third space loss compensation with 1000–1500 ml of crystalloid for up to a 500 ml loss followed by colloid infusion for greater losses), was associated with decreased postoperative morbidity [29]. More recently, however, Myles et al. showed in a large trial of over 3000 patients that there was no difference in long term outcome when comparing "restrictive versus liberal" approaches and that a restrictive approach could even be associated with a higher rate of acute kidney injury in high-risk patients during major abdominal surgery [31].

This fluid management controversy, which has spanned for over two decades, is in large part due to the lack of clear definitions of "restrictive" and "liberal". For example, the "restrictive" and "liberal" fluid regimens were completely different in the above studies. These subjective definitions thus depend on the arbitrary threshold each study design sets! A better approach would be to look at the question from another perspective: would it not be better to optimize the patient's cardiac preload by using an individualized goal-directed fluid strategy?

Heart-lung Interactions: Providing Reliable Goals For Fluid Therapy And Preload Optimization

Goal-directed therapy was initially limited by the invasiveness of pulmonary artery catheter monitoring [5, 7, 10]. Guiding fluid therapy based on transesophageal Doppler provided a much less invasive approach, but adoption was limited by its considerable learning curve. With the introduction of pulse contour technology derived from the heart-lung interactions, semi-invasive and non-invasive hemodynamic monitors became available for a broader application of GDHT both in the ICU and operating room [32, 33]. During mechanical ventilation, cyclic increase in intrathoracic pressure changes left ventricular preload and afterload. This pressure opposes cardiac venous return and reinforces systemic arterial blood flow away from the heart and out of the thorax. During expiration, the decrease in intrathoracic pressure has the opposite effect. This *reversed pulsus paradoxus* due to positive pressure ventilation is more prominent in hypovolemic patients and progressively decreases with correction of hypovolemia [34]. Once the patient's preload reaches the plateau of the Frank-Starling curve variations in blood pressure and flow due to heart-lung interactions become minimal.

The dynamic parameters derived from heart-lung interactions include pulse pressure variation (PPV), stroke volume variation (SVV), and Pleth Variability Index (PVI). All have been proposed as useful tools to guide preload optimizing strategies [34-36]. These dynamic parameters have been evaluated in multiple studies and are today an essential part of GDHT [37-39]. Even a new smartphone application, called Capstesia™ (Galenic App, Vitoria-Gasteiz, Spain), which automatically calculates PPV from a digital picture of the invasive arterial pressure waveform from any monitor screen, has been developed and tested to assess its ability to predict fluid responsiveness or decision making regarding fluid therapy [40-42]. This promising smartphone technology needs to be further evaluated to determine its potential role. Although heart-lung interactions provide a means for evaluating fluid responsiveness, several conditions, in addition to mechanical ventilation, are needed for the monitor to provide valid information. For pulse contour analysis, patients must have sinus rhythm, at least 8ml/kg (ideal body weight) of tidal volume for validated thresholds to be accurate, and a heart rate to respiratory rate ratio greater than 3.6. Arrhythmias, aortic regurgitation, sternotomy, thoracotomy, and right ventricular failure all negatively impact the capacity of these parameters to predict fluid responsiveness [43]. Under recognized conditions, SVV and PPV can predict fluid responsiveness (i.e. preload dependence) if their values are above 12-13% [44]. If the values are under 9%, patients are almost certainly no longer fluid responsive and additional fluids may be inadequate. For 25% of patients, however, there is a "gray zone" where SVV and PVV values between 9% and 12% may or may not predict fluid responsiveness [45].

Even with these limitations, multiple studies have shown the benefits of SV and CO optimization during non-cardiac surgery, emphasizing the importance of applying this strategy in high-risk patients [46, 47].

Despite the abundance of evidence on the benefits of using such dynamic indicators of fluid responsiveness to guide perioperative preload optimization strategies, most practicing anesthesiologists still only use static parameters such as blood pressure, heart rate, diuresis, and central venous pressure [48]. Static parameters do not predict fluid responsiveness consistently and cannot guide a GDHT strategy reliably [49]. Clinician skepticism and poor compliance to GDHT protocols have thus been a major limitation in improving care in high risk surgical patients.

From Evidence To Clinical Application: Passing Over The Compliance Hurdle

Although national and international societies now recommend implementing perioperative goal-directed hemodynamic and fluid therapy strategies [50, 51], many institutions still do not apply standardized criteria for hemodynamic optimization. Increasingly popular perioperative pathway models such as the Enhanced Recovery After Surgery (ERAS) and the Perioperative Surgical Home (PSH), however, encourage clinicians to apply GDHT [52, 53]. These programs push clinicians to be consistent in reducing variability and error through better coordination of care and increased evidence-based standardization. Both programs lead to improved clinical outcome, but their adoption, just like that of GDHT alone, remains low.

Many clinicians continue to arbitrarily administer fluids and this contributes to inconsistencies in patient care [54-56]. In fact, the major factor in determining the average volume of fluid given to surgical patients is whoever happens to be the assigned to that case. This leads to an unjustified variability in care and may negatively impact patient outcome [57]. The use of vasopressors is probably even more variable as there is still no consensus on perioperative blood pressure thresholds. Current perioperative hemodynamic therapy thus consists of poor adoption of appropriate end points and large inter-practitioner variability, which inevitably result in preventable complications related to hypo- or hyper-volemia and poor blood pressure control [58].

Although the reasons for clinician hesitation in utilizing GDHT strategies are complex, several issues reinforce this reluctance [48, 59]. Much of the literature consists of small studies and there is considerable variability in hemodynamic goals and types of included surgeries [60]. Larger multicenter studies have had inconclusive results and were often limited by a learning curve for each study center [61, 62]. For example, the OPTIMISE trial demonstrated the important impact of learning to apply GDHT. Postoperative outcome in the GDHT group only improved after correcting for the learning curve by removing the first 10 cases from each center [62]. Another limitation is the lack of awareness of the importance of perioperative optimization and the inability to maintain targets. Many anesthetists continue to have limited knowledge on hemodynamic variables and their appropriate use, which ultimately leads to low compliance with GDHT protocols [63, 64].

Knowledge and compliance are consequently the main limitations for applying GDHT. One approach that may facilitate adoption would be to automate therapy using a closed-loop or open-loop system. An automated system capable of administering GDHT can be seen as an extra pair of eyes and hands. The system observes the patient's hemodynamics, via a monitor, and then acts to maintain predefined goals, often via an automated infusion pump. This in no way exempts the clinician from the requirement of understanding hemodynamic variables and GDHT. The clinician will still need to determine appropriate targets, for example, but it does assure consistent compliance and limits the learning curve. The clinician is then free to focus on more important perioperative tasks that require human intelligence such as reasoning, problem solving, and making critical decisions while the automated system consistently adjusts hemodynamics. **Figure 1** depicts the evolution of perioperative GDHT over the past 40 years.

Increasing Compliance With Automation: The Example Of Fluid Therapy

Protocol adherence is essential to any goal-directed strategy, but consistent application is fastidious and does not seem to be feasible in the contemporary intraoperative setting where a single anesthetist is responsible for many tasks. An automated system offers an elegant way to integrate hemodynamic parameters, increase protocol compliance, and free the clinician to focus on other key intraoperative tasks. Closed-loops consist of a controller that monitors at least one parameter and automatically intervenes to maintain a predefined goal. They have been applied in medicine to manage neuromuscular blockade [65], narcosis [66], normoglycemia [67], mechanical ventilation [68], and more recently fluid administration [69, 70].

Several closed-loop fluid systems have been developed with various hemodynamic goals in the past 30 years. The first closed-loop fluid administration designs were guided by urine output and mean arterial pressure [71]. The advent of dynamic parameters of fluid responsiveness then led to the development of a new generation of closed-loop fluid systems, the first of which was validated in simulation [72, 73], animal [74], and finally human studies [75-80].

The closed-loop goal-directed fluid therapy system developed by Sironis (Irvine, USA) established the feasibility and safety of automated fluid administration (**Figure 2).** The interface allows both closed-loop [70, 81] and open-loop (i.e. decision support) [82] options. Both minimally-invasive [81] and non-invasive [77] pulse contour analysis technologies can guide the controller which uses two main components to interpret input data and administer fluids. The baseline component has two layers: a 'model' layer that predicts fluid response based on previous patient population data and an 'adaptive' layer that corrects bolus-based error after fluid administration. The second component, which adapts subsequent fluid infusion thresholds based on the patient's individual response to fluids, surpasses classical GDHT protocols by individualizing fluid therapy. Although it only takes into account the fluid component of GDHT (i.e. preload optimization), it increases protocol compliance and was associated with improved outcome when compared to fluid therapy based on a static parameters of fluid responsiveness [78]. In addition, when compared to manual goal-directed fluid therapy, this system maintains patients in a preload independent state for a longer period of time [81, 82]. The advantages of this system should not be ignored. It consistently gives fluids according to well established endpoints for any patient regardless of when or where it is used. This is not the same for anesthetists, who have been shown to be much less consistent in applying hemodynamic protocols. **Figure 3** shows all the closed-loop goal-directed fluid therapy studies done by our team since its conception.

Maintaining Perfusion Pressure With Closed-loop Vasopressor Infusion: The Next Step In Automation

Blood pressure control has challenged anesthetists for decades. Intraoperative hypotension is associated with poor end organ perfusion and results in increased patient morbidity and mortality [83]. To this day there is still no consensus on the exact definition of intraoperative hypotension and the best perioperative blood pressure goals to target. Futier et al. demonstrated that, in moderate-to-major abdominal surgeries, an individualized approach that maintained blood pressure within 10% of the patient's baseline value reduced the risk of postoperative organ dysfunction [84]. Maintaining an average predetermined value, however, is not the only challenge in blood pressure optimization. As high systolic blood pressure variability has been associated with increased postoperative mortality and renal failure [85], an effective vasopressor strategy should not only maintain a predetermined blood pressure value but also assure low variability. This requires frequent repetitive tasks and an automated system could outperform clinicians in maintaining a blood pressure target with minimal variability [86].

Several teams have developed closed-loop vasopressor systems. Ngan Kee et al. tested a closed-loop vasopressor system that administers phenylephrine based on non-invasive systolic blood pressure measurements [87]. The developed system has been extensively tested during obstetric anesthesia and, when compared to manually titrated phenylephrine, has been shown to provide better blood pressure control for hypotension associated with spinal anesthesia [88]. Sironis (Irvine, USA) has also recently developed another automated closed-loop vasopressor system that has extensively been tested in simulation [89, 90]. Recently, Joosten et al. demonstrated in a swine model of sodium nitroprusside-induced hypotension that the closed-loop system maintained mean arterial pressure at the 80 mmHg target with excellent performance metrics (i.e., target within ±5 mmHg for 98 ± 1% (mean ± SD) of the treatment time) [91]. Intraoperative and ICU studies are currently underway with promising preliminary results.

Automated vasopressor infusion is an attractive option for maintaining stable blood pressure and might represent the future for perioperative blood pressure management in complex cases [92, 93]. Although blood pressure is a key component of end organ oxygen delivery, adequate CO is also required. Excessive vasoconstriction will lead to increased systemic vascular resistance and inadequate flow. To avoid this "dry vasoconstriction", CO optimization with fluids should occur in parallel with vasopressors therapy. Closed-loop vasopressor management is the logical next step in GDHT automation, but there remains a significant need for additional research.

Fully Automated Goal-directed Hemodynamic Therapy: Its Future And Potential Limitations

Although there are a variety of ways to combine multiple closed-loop systems, the two main approaches refer to independent and interdependent technologies. An independent closed-loop setup has at least two closed-loop systems that work simultaneously without direct coordination while an interdependent closed-loop setup has a central controller that is capable of modifying all associated closed-loops. Most combined systems have used independent setups. Two research teams within the world of anesthesia have simultaneously combined both fluid and/or vasopressor administration [94, 95]. However, in recent years, several studies have shown the potential of interdependent GDHT automated systems in the management of acute heart failure [96], sepsis [95], and hemorrhage [94]. The future of closed-loop GDHT will probably consist of interdependent systems capable of interpreting, integrating, and optimizing the main determinants of CO and organ perfusion. Such systems do not exist yet, but some recent work has demonstrated that the simultaneous use of multiple physiological closed-loop systems operating in parallel is feasible (**Figure 4**) [97, 98].

Although automation increases GDHT compliance and may improve outcome in high-risk patients, several potential pitfall must be acknowledged. An automated system should never be left to itself or under the supervision of someone unable to understand the fundamental aspects of anesthesia, intensive care, hemodynamics, perfusion pressure, monitoring, pharmacology, and GDHT. Closed-loop systems should have safety cut-off points if a loss of input (e.g. monitoring dysfunction) or an inability to apply treatment (e.g. pump failure) occurs. The controller itself must have physiologic norms of CO and blood pressure that, if interpreted as inadequate or excessive, lead to treatment modifications. Despite these safety controls, an error in input, such as the arterial line pressure cell falling to the ground, would lead to an erroneous signal being interpreted as correct. In this situation of an increased hydrostatic pressure difference between the heart and the arterial line transducer, the controller would consider this erroneously high invasive blood pressure as adequate, decrease the vasopressor infusion, and the patient would suffer the negative effects of hypotension. An underestimation of blood pressure, due to an inappropriately elevated position of the arterial line transducer, could lead to excessive vasopressor infusion, hemorrhage, heart failure, and even death. Another source of potential danger that requires oversight is the closed-loop interventional component. Although drugs with similar effects could probably be interchanged and moderate dose differences in vasopressor or fluid composition would be corrected by the controller, administering the wrong drug, by switching the dobutamine and noradrenaline syringes for example, would lead to devastating consequences. Even if automated, GDHT will always require intelligent and knowledgeable oversight. Supplementary safety procedures, such as barcode recognition by the closed-loop pump of pre-filled syringes could be useful, but physicians remain the fundamental safeguard of these systems.

Conclusions

Perioperative GDHT has evolved from invasive “supra-physiological” maximization of oxygen delivery to minimally and non-invasively guided automated stroke volume optimization. Closed-loop systems provide an elegant approach for increasing compliance and implementing adaptive therapies that individualize treatment. Integration of multiple closed-loop setups into a universal interdependent system could represent the next step in optimizing end organ oxygen delivery. Finally, even with these advances in automation, physician oversight will remain essential to guarantee proper hemodynamic goals and assure perioperative safety.

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Figures

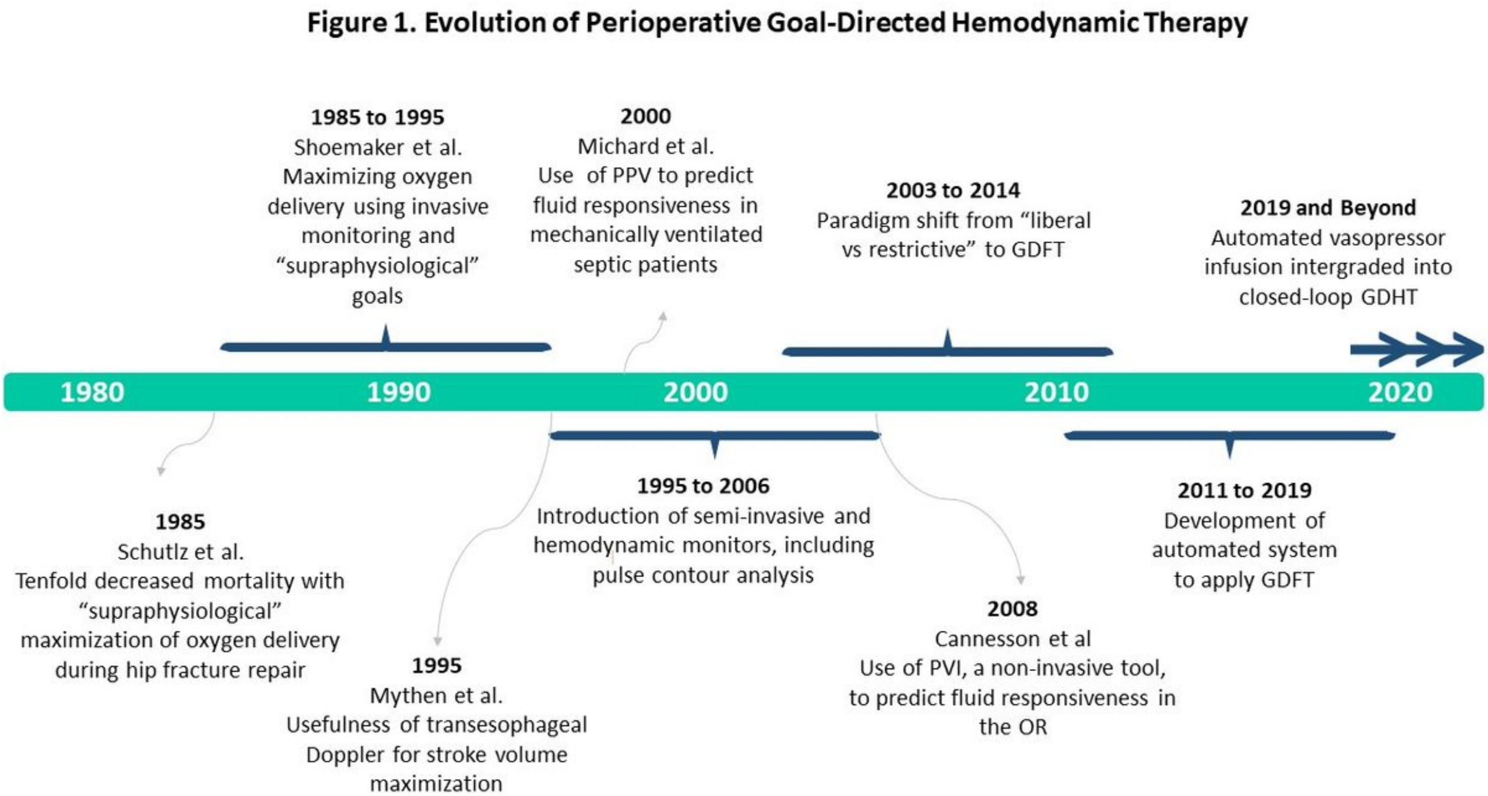

Figure 1

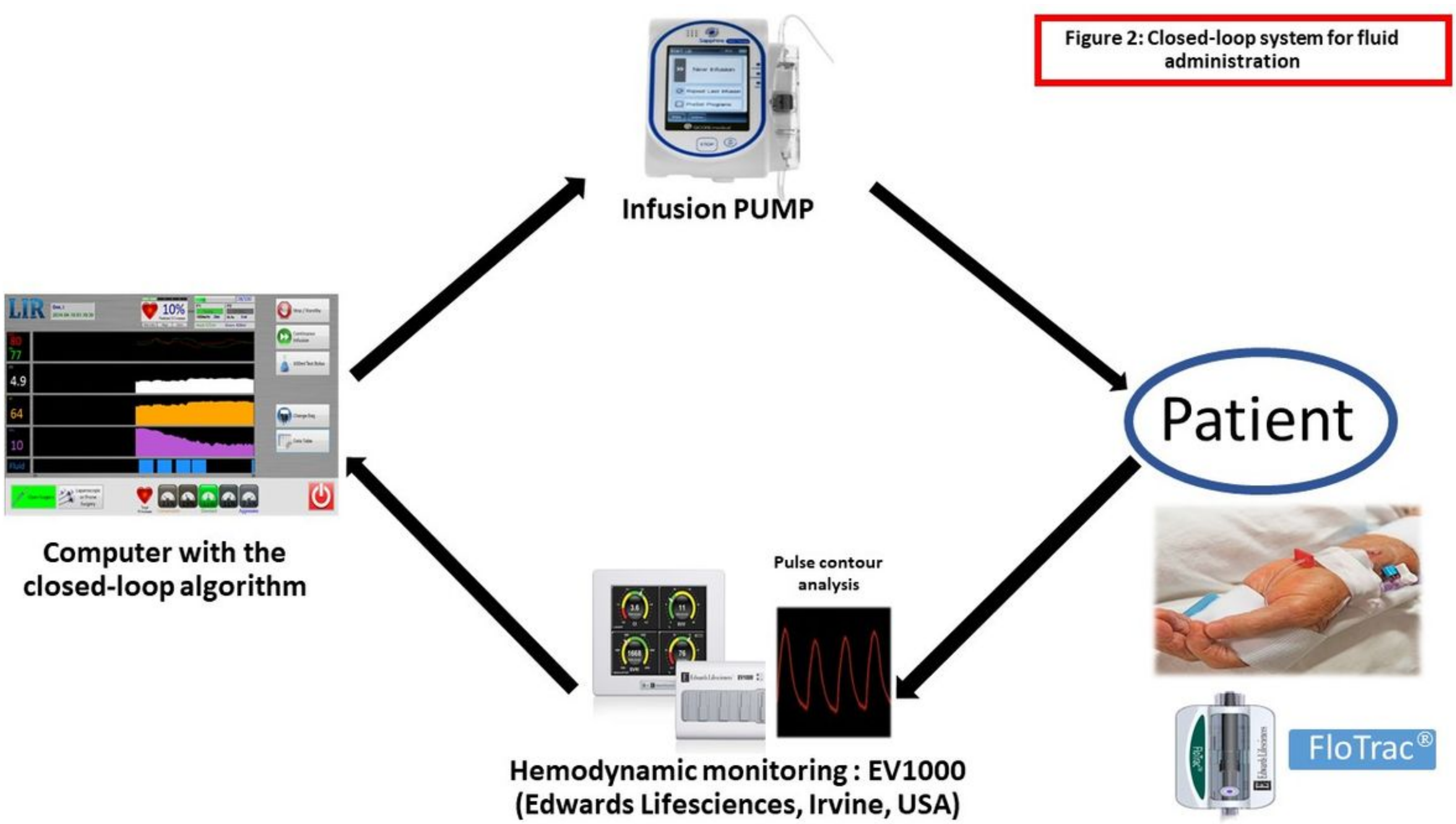

Figure 2

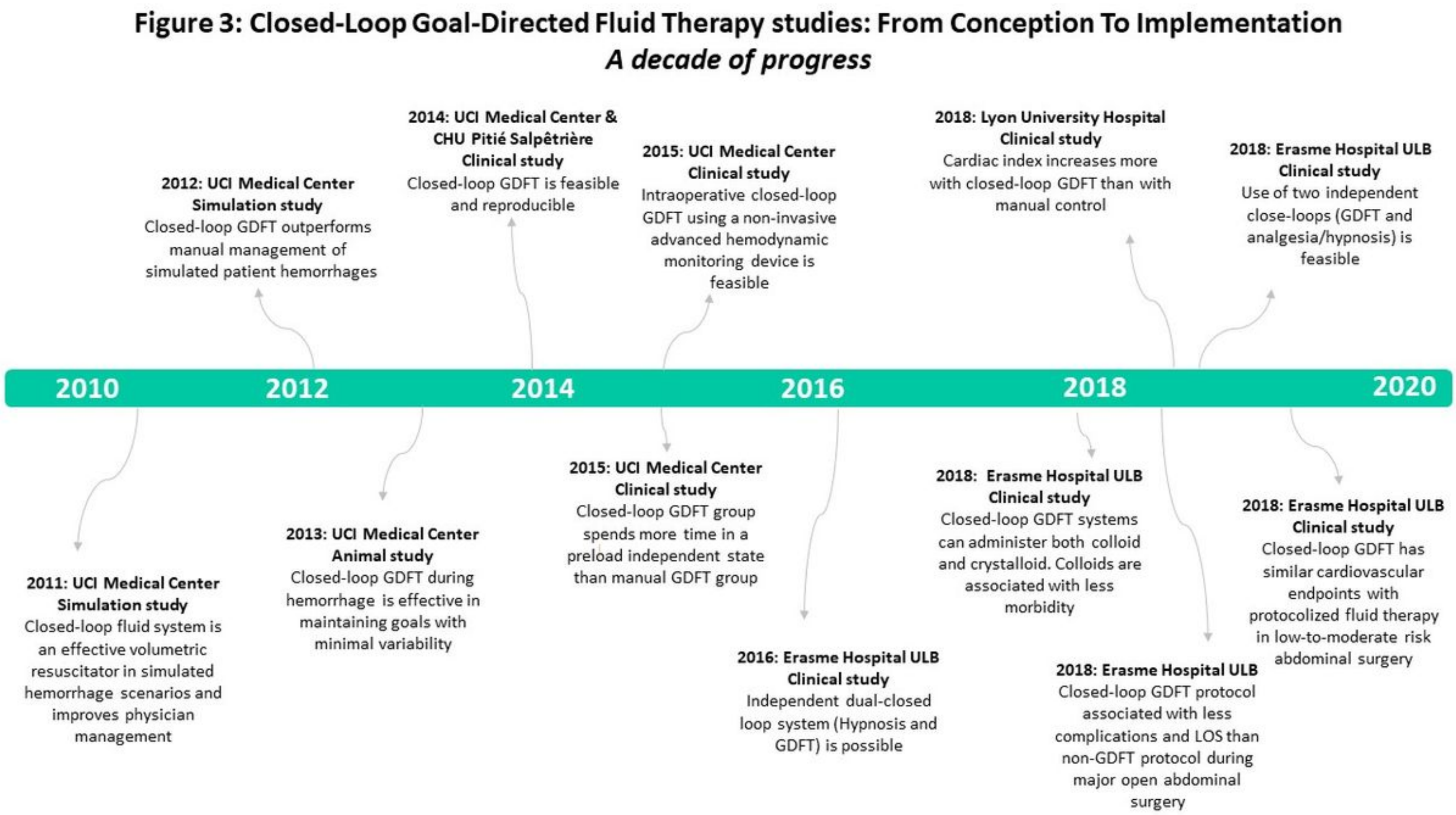

Figure 3

Figure 4

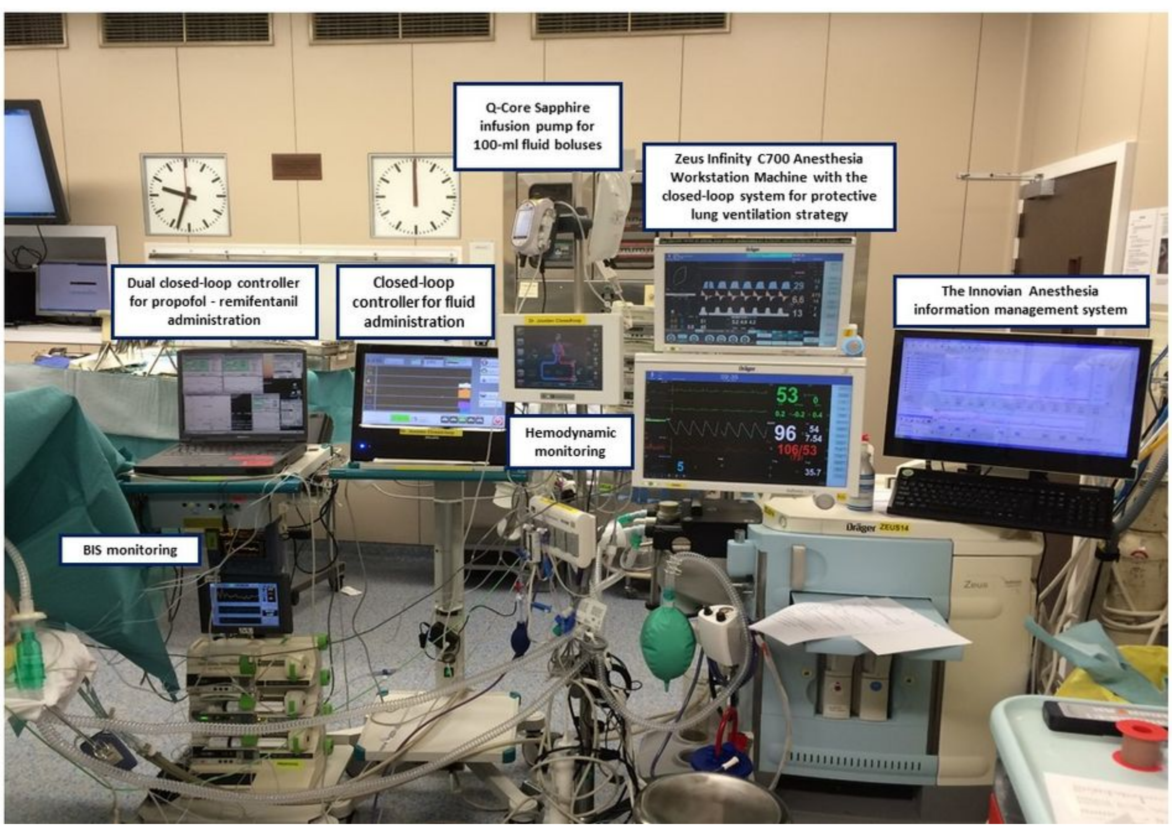

Figure 4