Goal-Directed fluid therapy with closed-loop assistance during moderate risk surgery using noninvasive cardiac output monitoring: A pilot study

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Editor’s key points

- Goal-directed fluid therapy is known to improve outcome after high risk surgery.
- Closed loop (feedback) control systems are increasingly being implemented in medical devices.
- The authors have developed a closed loop system implementing feedback control of goal-directed fluid administration.
- The current study investigated the feasibility of using signals obtained from a noninvasive cardiac output monitor.

Background. Goal directed fluid therapy (GDFT) has been shown to improve outcomes in moderate to high-risk surgery. However, most of the present GDFT protocols based on cardiac output optimization use invasive devices and the protocols may require significant practitioner attention and intervention to apply them accurately. The aim of this prospective pilot study was to evaluate the clinical feasibility of GDFT using a closed-loop fluid administration system with a non-invasive cardiac output monitoring device (Nexfin™, BMEYE, Amsterdam, Netherlands).

Methods. Patients scheduled for elective moderate risk surgery under general anaesthesia were enrolled. The primary anaesthesia team managing the case selected GDFT targets using the controller interface and all patients received a baseline 3 ml kg⁻¹ h⁻¹ crystalloid infusion. Colloid solutions were delivered by the closed-loop system for intravascular volume expansion using data from the Nexfin™ monitor. Compliance with GDFT management was defined as acceptable when a patient spent more than 85% of the surgery time in a preload independent state (defined as pulse pressure variation <13%) or when average cardiac index during surgery was >2.5 litre min⁻¹ m⁻².

Results. A total of 13 patients were included in the study group. All patients met the established criteria for delivery of GDFT for greater than 85% of case time. The median length of stay in the hospital was 5 [3–6] days.

Conclusion. In this pilot study, GDFT management using the closed-loop fluid administration system with a non-invasive CO monitoring device was feasible and maintained a high rate of protocol compliance.

Clinical trial registration. NCT02020863.

Keywords: cardiac output; monitoring; noninvasive; safety

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Perioperative haemodynamic optimization using goal-directed fluid therapy (GDFT) has been correlated with improved postoperative outcomes following moderate to major risk surgeries and is becoming a standard of care in the anaesthesia setting. The evidence supporting GDFT has been sufficiently strong that national recommendations by the UK, France and other European countries have been implemented. The most significant progress has been made in the UK where the National Institute for Health and Clinical Excellence (NICE) released a technology guideline in 2011 recommending the use of cardiac output monitoring and optimization for perioperative GDFT in high-risk surgical patients. Despite these recommendations, widespread implementation of GDFT has not been widely accepted into clinical practices.

One of the reasons for this lack of adoption may be that GDFT protocols are time- and attention-consuming and it has been established that even under study conditions, complete adherence to protocol is often not greater than 50%. Additionally, measurement of cardiac output has traditionally been associated with the use of additional invasive or minimally invasive monitoring devices requiring the placement of an arterial line which is not always desirable because of the potential complications associated with its invasiveness. The recent development of non-invasive cardiac output monitoring devices is a suitable alternative for patients who are not equipped with an arterial line and...
may expand the potential application of GDTFT strategies in the surgical setting.

As this evidence based approach to fluid management becomes more accepted among leading institutions, the next challenge will be to close the gap between evidence based, international recommendations, and best clinical practice. Our group has been developing a novel automated closed-loop fluid administration system, which is designed to assist anaesthesia providers by easing implementation of GDTFT protocols in the perioperative period. The system has been previously tested in simulation,15,16 engineering,17 animal studies,18 and even in a clinical study.19 In our previous multicenter pilot study,19 we had described the first use of this automated closed-loop system in patients undergoing high risk surgery (major aortic vascular and hepatobiliary surgeries).

The aim of this current prospective pilot study was to assess the clinical feasibility of the closed-loop system to provide high-compliance GDTFT while using a completely non-invasive cardiac output monitoring system in patients undergoing moderate risk surgery. Compliance with GDTFT management was defined as acceptable when a patient spent more than 85% of the surgery time in a preload independent state (defined as pulse pressure variation <13%) or when average cardiac index during surgery was >2.5 litre min$^{-1}$ m$^{-2}$, consistent with our previous pilot study.19

**Methods**

Ethical approval was obtained from the University of California, Irvine Institutional Review Board (HS#2011-8554) and the study was registered with ClinicalTrials.gov (protocol ID NCT02020863). Written informed consent was obtained from 13 patients with ASA physical status II to III, aged 18 yrs or older, scheduled for moderate risk surgery for more than 2 h (including elective hip arthroplasty, colorectal and major gynaecological procedures) between February 2014 and May 2014, for which the primary anaesthesia team planned to use a general anaesthetic and non-invasive monitoring. Exclusion criteria were patients under 18 yrs of age, pregnant, body mass index >35 kg m$^{-2}$, presence of moderate to severe cardiac valvular disease, cardiac arrhythmias, left ventricular ejection fraction <40%, right ventricular failure and known allergy to 6% hydroxyethyl starch 130/0.4 or 5% serum Albumin. In addition, per Institutional Review Board requirements, patients were not recruited if the principal investigator was part of the primary anaesthesia team because of the possibility of any conflict of interest. A member of the research staff who had experience with operating the closed-loop system was present in the OR throughout all surgical cases to assist the primary team with the system as needed.

**Anaesthesia protocol**

All patients received the standard of care at our institution including a multidisciplinary team approach known as ‘Perioperative Surgical Home’.20,21 Patients were equipped with two peripheral IVs and were monitored with an electrocardiogram, pulse oximetry, non-invasive blood pressure (NIBP), end-tidal carbon dioxide partial pressure and temperature (oesophageal temperature probe). All subjects had additional non-invasive continuous arterial pressure and cardiac output monitoring via the NexfinTM device planned as part of their anaesthetic care. According to the manufacturer’s recommendations, the pneumatic cuff was placed on the middle phalanx of the second, third or fourth finger and was zeroed to atmospheric pressure at the level of the mid-axillary position.

Anaesthesia was induced with fentanyl (2 µg kg$^{-1}$), propofol (2 mg kg$^{-1}$) and rocuronium (0.6 mg kg$^{-1}$) to enable oral endotrachial intubation. Maintenance used oxygen-enriched air with sevoflurane (0.8 to 1.2 MAC) and fentanyl boluses (1 µg kg$^{-1}$ every 30–45 min) at the discretion of the anaesthesia team. All patients were mechanically ventilated using a volume-controlled mode with a tidal volume at 8 ml kg$^{-1}$ of ideal body weight and a respiratory rate adjusted to achieve normocapnia (end tidal CO2 between 4.3 and 4.8 Kpa) without positive end-expiratory pressure. A forced-air warming (3 M™ Bair Hugger™, St. Paul, Minnesota, USA) and a blood-fluid warming system (3 M™ Ranger™, St. Paul, Minnesota, USA) were used to minimize intraoperative hypothermia. The closed loop and the Nexfin™ monitoring were started immediately following completion of the anaesthesia induction.

Postoperative analgesia was provided by epidural infusion (placed by the pain service prior to coming to the operating room) or intravenous infusion of morphine at the discretion of the primary anaesthesiologist. The epidural was not activated (save for a 3 ml test-dose of 2% lidocaine with 1:200 000 epinephrine) until final closure of the surgical case and end of data collection.

**Nexfin™ device**

The Nexfin™ monitor (BMEYE, Amsterdam, Netherlands) is a completely non-invasive photoplethysmographic technology that offers the ability to monitor cardiac output, and respiratory variations in pulse pressure (PPV) continuously. Others parameters measured by this monitor include continuous blood pressure (systolic, diastolic, mean),22 heart rate (HR), stroke volume (SV), systemic vascular resistance (SVR), and an index of left ventricular contractility (dp/dt).

**Closed-loop system set-up**

The closed-loop software developed at UCI was run on a Shuttle X50 Touchscreen PC (Shuttle Computer Group, City of Industry, CA) running Windows 7 (Microsoft Corp, Redmond, CA). Software version 4.6 L was used for this study. The system was connected via a USB-to-serial adapter to an analog-to-digital converter which captured the analog output of the Nexfin™ device. The four channels available on the Nexfin™ analog output were set to transmit mean arterial pressure (MAP), HR, SV, and PPV. Cardiac output and approximated SVR were calculated from these four inputs inside the closed-loop software.
A Q-Core Sapphire Multi-Therapy Infusion Pump (Q-Core, Netanya, Israel) was used by the closed-loop to deliver fluid boluses. The Sapphire pump is a single-channel volumetric pump capable of flow rates from 0.1 to 999 ml per hour. The pump was controlled by the closed-loop system using software provided by Q-Core via serial connection (Commands Server R.01).

Closed-loop system description
The closed-loop system has been described extensively in previous publications. As a brief overview, the aim of this system is to optimize patients’ fluid status and SV to reach the plateau of the Frank-Starling curve relationship and then maintain that plateau throughout surgical time, in accordance with GDFT principles. To achieve this goal, the closed-loop system monitors SV, HR, MAP, cardiac output and a dynamic predictor of fluid responsiveness. The controller has been designed to be error-correcting during direct fluid management to detect and adapt to changes induced by surgical and anaesthetic conditions. The final action actually taken by the controller is determined by a rule-based layer after processing in the previous model and adaptive layers. The system delivers 100 ml fluid boluses over 6 min and evaluates patient response after each infusion; the controller is therefore designed for GDFT optimization rather than acute volume resuscitation or haemorrhage management.

The primary anaesthetist was responsible for the selection of resuscitation targets throughout the case. The standard set point was to seek an average 15% increase in stroke volume following a 500 ml bolus, scaled down for the smaller 100 ml boluses actually delivered. The primary anaesthetist had the option of changing the target set point from 7.5 to 23%, allowing for a more liberal or conservative fluid management strategy respectively. The closed-loop controller interface also includes the ability to manually deliver boluses as well as stop boluses or go to ‘monitor only’ operation. Programmed alerts, both visual and audio, notify the anaesthetist when each fluid bolus is delivered as well as any system alerts or notifications.

Fluid administration protocol
All patients had a baseline crystalloid infusion of 3 ml kg⁻¹ h⁻¹ on a separate fluid pump throughout the surgical case. In addition to this maintenance infusion, the closed-loop system delivered colloid boluses with the specific fluid chosen by the primary anaesthetist. No attempt was made to standardize the choice of colloid. Available intravenous solutions were 6% hydroxyethyl starch (HES) 130/0.4 (Voluven®, Fresenius Kabi, Frankfurt, Germany) or 5% serum albumin (Grifols, Sant Cugat del Valles, Barcelona). The closed-loop system was started after induction of anaesthesia and stopped when the anaesthetist provider began emergence or the patient was allowed to spontaneously ventilate. No transfusion triggers were predefined in the study protocol and packed red blood cell (PRBC) administration were delivered to patients independently from the closed-loop system at the discretion of the anaesthesia team.

Variables are presented as mean standard deviations (SD) or median (25–75th percentile) as appropriate for normal and non-normal data, respectively. The following variables were collected and analysed during the surgical cases: duration of surgical case, estimated blood loss (EBL), total urine output (UO), total crystalloid, colloid and blood administration, as well as haemodynamic (MAP, HR, SV, CO, PPV) which were saved every 4 s by the closed-loop system. Fluid balance was calculated as: (total crystalloid + colloid + blood) – (EBL + UO). We also recorded the total ephedrine and phenylephrine administration, and the hospital length of stay.

Results
Demographic characteristics of the patients
Thirteen patients were included in the study over the four months study period. Data of the thirteen patients are summarized in Table 1. The patients included six males and seven females. Seven patients were referred for colorectal surgery, three for hip arthroplasties and three for major gynaecology procedures.


Fluid management and haemodynamic data
GDFT with closed-loop assistance was successful in meeting the target criteria in all patients. The closed-loop system administered a total of 74 intraoperative fluid boluses of 100 ml over the 13 study cases. The minimum given in a case was 1 bolus and the maximum was 20 boluses. The primary anaesthetists in charge of the surgical cases never stopped the system.

Haemodynamic variables during these thirteen cases are presented in Table 2.

Average cardiac index was 2.9 l min⁻¹ m⁻² and on average, patients spent 96.3% (range 84.76 to 100%) of surgery time in a preload independent state.

Figure 1 show SV, PPV and fluid administration by the closed-loop during an illustrative bleeding complicated surgical case.

Estimated blood loss was 150 [25–250] ml, and urine output was 483 [263–633] ml. Total crystalloid administration was 1451 [1034–2151] ml and total colloid administration was 500 [150–500] ml. Twelve patients received albumin boluses and one patient received 6% hydroxyethylstarch 130/04 boluses for GDFT. Two patients received blood transfusion secondary to operative blood loss. The mean fluid balance was 1535 [1113–2075] ml.

All patients were extubated in the operating room at the completion of the case.
No patient was reintubated. The median length of stay in the hospital was 5 [3–6] days.

**Discussion**

This pilot study reports the first use of the closed-loop fluid administration system to assist clinicians in providing GDFT using a completely non-invasive cardiac output monitoring device in patients undergoing moderate risk surgery. The closed-loop system was able to conduct GDFT optimization in 13 of the 13 included patients with an average of 96.3% of patient’s surgery time spent in a preload independent state (defined as PPV < 13%) or when average cardiac index during the case was ≥2.5 litre min⁻¹ m⁻². As there is no existing consensus for the definition of compliance to GDFT during surgery, we chose a cardiac index of 2.5 litre min⁻¹ m⁻² because it has been used in several studies as target for GDFT. In the same way, PPV, reflecting the cyclic changes in preload induced by mechanical ventilation, has also been shown to be a strong predictor of fluid responsiveness.

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Overall, the closed-loop system's performance was consistent with expected fluid management given the clinical progress of the surgical cases it was managing. For example, during a ‘routine’ case with minimal blood loss the system delivered minimal additional fluid, whereas in a more ‘complicated’ case with high blood loss it delivered fluid consistently to

### Table 1  Case Summary information. EBL, Estimated blood loss; UO, Urine output; PRBC, Packed red blood cells. 25th IQ: 25th Interquartile; 75th IQ: 75th Interquartile

<table>
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<th>Age (yrs)</th>
<th>Time (min)</th>
<th>EBL (ml)</th>
<th>UO (ml)</th>
<th>Crystalloid (ml)</th>
<th>Colloid (ml)</th>
<th>PRBC (unit)</th>
<th>Fluid balance (ml)</th>
<th>Ephedrine (mg)</th>
<th>Phenylephrine (μg)</th>
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### Table 2  Mean hemodynamic data. Data are expressed as mean (SD). HR, heart rate; MAP, mean arterial pressure; PPV, pulse pressure variation; SV, stroke volume; SVI, stroke volume index

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<tr>
<th>Case</th>
<th>HR (bpm)</th>
<th>MAP (mmHg)</th>
<th>Cardiac index (L min⁻¹ m⁻²)</th>
<th>PPV (%)</th>
<th>SV (ml)</th>
<th>SVI (ml m⁻²)</th>
<th>% surgical time in preload independent state</th>
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maintain intravascular volume. For example, patient 3 (Fig. 1) was a complicated redo of a hip arthroplasty and this patient lost almost 2000 ml of blood throughout the nearly seven hours of surgery time. This difference in delivery was with the same standard setpoint (15%) for the controller in both cases, so was not a result of supervisor modification of the system but rather the system responding to the clinical data it was reading from the non-invasive cardiac output monitor. The results support the hypothesis that the closed-loop may be able to provide consistent implementation of GDFT principles with minimal additional clinician workload by performing repetitive and time-consuming tasks while allowing the physician to focus on higher-level aspects of care.

The recent ‘OPTIMISE’ trial, reported the results of a multicenter study of 734 high-risk patients undergoing gastrointestinal surgery which were randomized to receive usual care or GDT using a cardiac output monitoring device requiring an arterial catheter for pulse pressure analysis. The trial showed a lower incidence of postoperative complications in the GDT group ($P = 0.07$). However, when the results were adjusted for protocol adherence (exclusion of the first 10 patients of each centre), they showed a more robust treatment effect (43.4 vs 68% from preliminary data). These preliminary higher complications rates might be explained by low protocol compliance and a learning curve that required the application of such a GDT protocol. A closed-loop system may thus be beneficial to improve GDFT protocol compliance.

As GDFT requires a monitor and an intervention (volume expansion), the use of a non-invasive cardiac output monitoring such as the Nexfin™ may expand the potential patient pool in whom GDFT may be applied as compared with invasively monitored patients alone. Furthermore, despite the limitations inherent in the current generation of non-invasive CO monitoring devices, the use of any such system may still be beneficial for patients who would be otherwise ‘not monitored’. This is even more necessary in cases when an arterial catheter is not indicated or problematic and in surgical procedures involving important fluid shifts and rapid haemodynamic changes. In these specific cases, we often want to measure continuously and in real-time the haemodynamic effects of our therapeutic interventions in order to appropriately adapt or improve our clinical decisions making.

Lastly, according to the Frank-Starling cardiac curve relationship, the concept of fluid responsiveness is usually defined as a 15% increase in cardiac output or SV after a fluid challenge over 10–30 min. In our study, the standard set point was to seek an average 15% increase in SV following a 500 ml bolus, scaled down for the smaller 100 ml boluses actually delivered. This means that the system is looking for a rise of 3% or more in cardiac output or SV based on the 100 ml fluid bolus. Some may suggest that 3% is beyond the absolute accuracy of any device measuring cardiac output, but our experience with GDFT and in particular the closed loop system has suggested that these small volumes are adequate to determine whether or not the patient will respond to fluid administration. In our in-vivo animal study, some of the fluid boluses were 100 ml and some were 250 ml. We found that if the cardiac output or SV did not rise within the first 100 ml of fluid, it was extremely unlikely that the remaining 150 ml of a 250 ml bolus would cause it to rise. This can be explained by the form of the Frank-Starling relationship where the increase in stroke volume theoretically would be greater in the steep portion of the curve at the beginning (in particular, the first 100 ml) of the fluid challenge. The extra fluid in these boluses did not provide any
Goal-Directed fluid therapy with closed-loop assistance

additional information to the closed-loop and only served to contribute to overloading over the course of the case. We have concluded that despite the limitations in the minimally and/or non-invasive systems, 100 ml is usually sufficient to cause a positive change in the measurement if the patient is going to respond at all. Around the same time, Muller and colleagues published their mini-fluid challenge manuscript which helped validate our observations. In this study, the mini-fluid challenge technique (infusion of only 100 ml of colloids over 1 min) was found to predict fluid responsiveness of a full fluid challenge.

Limitations

This study is a small pilot series using a completely non-invasive monitoring system. However, based on our previous published clinical study,13 13 patients is a sufficient sample for simple demonstration of feasibility. Future studies will be needed with a control group of patients receiving a manually driven GDFT protocol for comparison. Secondly, as any closed-loop system is inherently dependent on the accuracy of the sensors used to measure the controlled variable, the limits of non-invasive technology should be acknowledged, and ultimately validation of our results at other centres and in larger randomized studies is warranted. Other clinical studies are also necessary to further assess the clinical ability of the closed-loop for GDFT in different sub-populations of patients to understand how it may be impacted by perturbations in physiology. Finally, the voluntary exclusion of blood product administration from the closed-loop may be considered a potential limitation, but the risk assessment and trial design of closed-loop blood administration was well beyond the scope of this project.

Conclusion

Based on the results of this pilot study, GDFT using the closed-loop fluid administration system with a non-invasive cardiac output monitoring device is feasible and met the defined target criteria in all patients.

Authors’ contributions

A.J.: recruited patients, collected and analysed data, drafted the final manuscript. T.H.: recruited patients, collected and analysed data, drafted the final manuscript. K.S.: analysed the data and drafted the final manuscript. C.C.: designed the study and the closed-loop system, analysed the data and drafted the final manuscript. M.C.: designed the study and the closed-loop system, analysed the data and drafted the final manuscript. J.R.: designed the study and the closed-loop checking and administration protocol. All authors read and approved the final manuscript.

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Declaration of interest

Maxime Connesson is a consultant for Edwards Lifesciences (Irvine, CA, USA), Covidien (Boulder, CO, USA), Philips Medical System (Suirenes, France), and Fresenius Kabi (Sevres, France). Maxime Connesson and Joseph Rinehart are co-founders of Sironis and own patents on close loop fluid management and haemodynamic optimization.

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