Fluid responsiveness in the postoperative period: a prospective study in non-critically ill patients

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Abstract

Background:

The incidence of Fluid Responsiveness (FR) in non-critically ill surgical patients and the proportion of patients in whom Stroke Volume (SV) significantly increases after a bolus of intravenous fluids (Volume Expansion, VE) are unknown after surgery. Although being Fluid Responder (FRer) does not necessarily imply being hypovolemic, it remains to be determined whether postoperative FR is associated with complications.

Objectives:

The aims of this prospective study are to determine 1) the incidence of FR in non-critically ill surgical patients after major surgeries, 2) if postoperative FR is associated with and predicts 30-day complications, 3) the proportion of patients in whom SV significantly increases after VE.

Methods:

Ethical approval: 14-452-SDR; ClinicalTrials.gov number, NCT02418663. Adult patients undergoing major thoracic or abdominal surgery, not requiring intensive care unit admission, and treated with a surgery-specific Enhanced Recovery Program were enrolled. FR was assessed soon after surgery, and daily for the first 48 h. SV was measured with the ccNexfin® just before and 1 min after a fluid challenge (FC) with 250 ml of Lactated Ringer's over 5 min. FR was also assessed "on call" when VE was clinically deemed. A patient was considered fluid responder (FRer) if SV increased by 15% either 1 min after the FC or 1 min after VE, at least 1 time within 48 h. Treating physicians were blind to all SV measurements.

Results:

FR after a FC was present in 52 over 172 patients (30.2%). Complications occurred in 53.8% of FRer and in 45% of non-FRer (Relative Risk, $RR_{crude} = 1.19$, 95% Confidence Interval, $CI = 0.86$ to 1.64 , $p\text{-value} = 0.286$; $RR_{adjusted} = 1.08$, 95% $CI = 0.68$ to 1.70 , $p\text{-value} = 0.719$). After controlling for confounders (age, duration of surgery, intraoperative blood loss and volume of intravenous fluids, and postoperative negative fluid balance) FR was not an independent predictor of complications (Odds Ratio, $OR_{crude} = 1.16$ 95% $CI = 0.68$ to 2.01 , $p\text{-value} = 0.579$; $OR_{adjusted} = 0.98$ 95% $CI = 0.42$ to 2.26 , $p\text{-value} = 0.965$). "On call FR" was measured in 15 patients (8.7%); of these, only 4 (26.7%) were FRer.

Conclusions:

Thirty percent of non-critically ill surgical patients are FRer after surgery. After controlling for confounders, FR is not associated with and it does not predict 30-day complications. Finally, fluid boluses administered on the basis of clinical signs of hypovolemia rarely determine a significant increase of SV and might be potentially harmful.

Résumé

Avant-propos :

L'incidence de la Réponse au Remplissage Vasculaire (RRV) chez les patients chirurgicaux non critiques et la proportion des patients dans lesquels le Débit Systolique (DS) augmente significativement après d'un bolus de fluides intraveineuses (Expansion Volémique, EV) ne sont pas connus après de la chirurgie. Bien qu'être Répondeur aux remplissage vasculaire (ReurRV) n'implique nécessairement être hypovolémique, il reste encore à déterminer si la RRV postopératoire soit associée avec des complications.

Objectif :

Cette étude perspective est ciblée à déterminer 1) l'incidence de la RRV en patients chirurgicaux non critiques après des chirurgies majeures, 2) si la RRV postopératoire est associée et prédit les complications dans les 30 jours, 3) la proportion des patients dans lesquels le DS augmente significativement après la EV.

Méthodologie :

Approbation éthique : 14-452-SDR ; numéro ClinicalTrials.gov, NCT02418663. Les patients adultes subissant une chirurgie thoracique ou abdominale majeure, ne nécessitant pas d'admission en unité de soins intensifs et traités avec un Programme de Plans de Soins périopératoires (ERAS), ont été inscrits. La RRV a été évaluée peu après la chirurgie, et quotidiennement pendant les 48 premières heures, le DS a été mesurée avec le ccNexfin® juste avant et puis 1 min après d'un Fluid Challenge (FC) avec 250 mls of Lactated Ringer's pendant 5 min. La RRV a également été évalué « sur appel » lorsque la EV a été cliniquement jugé. Un patient était considéré comme ReurRV si le DS augmentait de 15% soit 1 min après le FC, soit 1 min après l'EV, au moins 1 fois en 48 h. Les médecins traitants étaient aveugles à toutes les mesures du DS.

Résultats :

RRV après le FC était présent dans 52 patients sur 172 (30,2%). Des complications sont survenues dans 53,8% des cas et dans 45% des cas non ReurRV (risque relatif, $RR_{crude} = 1,19$, intervalle de confiance à 95%, IC = 0,86 à 1,64, $p = 0,286$, RR ajusté = 1,08, IC à 95% = 0,68 à 1,70, valeur $p = 0,719$). Après d'un contrôle des facteurs confusionnels (âge, durée de la chirurgie, perte de sang peropératoire et volume des liquides intraveineux, bilan liquidien postopératoire négatif), RRV n'était pas un prédicteur indépendant des complications (Odds

Ratio, ORcrude = 1.16 IC 95% = 0.68 à 2.01, p valeur = 0,579; ORajusté = 0,98 IC à 95% = 0,42 à 2,26, valeur p = 0,965). EV était mesurée chez 15 patients (8,7%) ; parmi ceux-ci, seulement 4 (26,7%) étaient ReurRV.

Conclusions :

30% des patients chirurgicaux non critiques sont ReurRV après l'opération. Après le contrôle des facteurs confusionnels, la RRV n'est pas associée et ne prédit pas des complications à 30 jours. Enfin, les fluides administrés sur la base de signes cliniques d'hypovolémie déterminent rarement une augmentation significative des DS et pourraient être potentiellement nocifs.

Preface

Contributions of authors

Dr Gabriele Baldini provided supervision and guidance for the study. Dr Silvia Cicala performed the literature review. Dr Silvia Cicala performed also enrollment, assessments and data collection, to which (for the initial phase of the study) Dr Sergio Cocimano and Dr Mattia Portinari contributed. Dr Silvia Cicala and Dr Gabriele Baldini performed the final statistical analysis of this study. Dr Gabriele Baldini made substantial contribution to study conception and design as well as interpretation of data.

This study was conducted at the Montreal General Hospital of the McGill University Centre (Montreal, QC, Canada). Edward Lifesciences (Irvine, CA) provided the ccNexfin® monitors. Finger cuffs for this study were purchased with private funding of Dr Baldini. Edward Lifesciences was not involved in the design of this study and had no role during its execution, data storage, analyses and/or interpretation of the data. Overall, Edward Lifesciences did not influence the trial and its results in any way or form.

Claims of originality

The present thesis yielded new knowledge by:

- (1) determining the incidence of FR in non-critically ill surgical patients after major surgeries.
- (2) establishing that postoperative FR is not associated with and does not predicts 30-day complications.
- (3) identifying the proportion of non-critically ill surgical patients admitted on surgical in whom SV significantly increases after VE.

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CHAPTER 1

FLUID RESPONSIVENESS IN THE POSTOPERATIVE SETTING

1. Enhanced Recovery Programs

In the last few decades, the introduction of Enhanced Recovery Programs (ERPs) after surgery has significantly reduced patients' hospitalization time and overall complications without increasing readmission rates¹⁻³. These programs contain a variety of perioperative strategies aimed at reducing surgical stress and accelerating surgical recovery (Fig.1)². Traditional perioperative care is provided in clinician-focused expertise silos, with the patient moving from one clinician to the next. A fundamental paradigm shift with ERPs is the reorganization of perioperative care around the patient, integrating the elements of perioperative care into a single pathway.

Optimal perioperative fluid management is one of the key elements of ERPs, as both perioperative fluid and sodium excess, and tissue hypoperfusion, have been shown to increase complications and delay surgical recovery⁴. In the traditional approach, intraoperative fluid therapy is under the direct control of the anesthesiologists, while postoperative fluid management is controlled by the surgeons. However, hemodynamic changes such as decreased systemic vascular resistance and increased endothelial permeability persist into the postoperative period and can mislead physicians to administer intravenous fluids when not necessary. Thus, the benefits of judicious intraoperative fluid therapy may be invalidated by postoperative decisions, and conversely, poor intraoperative fluid management may require ongoing postoperative resuscitation. In the context of an ERP, in order to improve patients outcomes, there is an opportunity to better integrate the aspects of fluid therapy, traditionally managed separately between different clinicians, with the phases of perioperative care.

Figure 1 ERAS elements³.

2. Perioperative Fluid Management

A judicious administration of intraoperative fluids has increasingly shown to improve postoperative outcomes⁵. Although a variety of different fluid regimens have been studied in the intraoperative and immediate postoperative period, data on approaches to appropriate fluid management in the remainder of the postoperative setting are scarce. In the postoperative framework, however, Lowell and colleagues⁶ demonstrated that 40% of surgical patients admitted to the intensive care unit (ICU) had a significant (>10%) weight gain compared to preoperative or premorbid value. This increase was attributed to superfluous perioperative fluid administration, and was associated with more morbidity and mortality, as well as a greater length of ICU stay. Similar results have been seen in patients admitted on surgical wards after surgery, in whom a dose-response relation between complications and increasing volumes of intravenous fluid, as well as increasing body weight on the day of operation was found⁷. Even a modest salt and water balance resulting in positive weight gain of 3 Kg was associated with complications after colonic surgery⁷. Furthermore, Gustafsson et al. found

that any additional liter of fluids administered the day of surgery was associated with an increased risk of complications (OR =1.32, 95% CI= 1.17-1.50).⁸ These findings are consistent with the widespread recognition that administering fluids without objective evidence of hypovolemia disrupts endothelial permeability⁵. In fact, a state of hypervolemia increases intravascular hydrostatic pressure that triggers the release of atrial natriuretic peptides, directly damaging the endothelial glycocalyx⁹. As a result, fluid shifts out the circulation and accumulates in the interstitial space. Accumulating excessive perioperative volume may disrupt cardiopulmonary function, wound healing, coagulation, tissue oxygenation, and recovery of gastrointestinal motility¹⁰. Clinically, such derangements may manifest as myocardial ischemia, pulmonary edema, respiratory failure, paralytic ileus, electrolyte disturbances, abdominal compartment syndrome, and sepsis¹⁰. Arieff additionally suggested that pulmonary edema may often be the first observed sign of fluid overload in post-surgical patients¹¹. He advocates that commonly recorded clinical parameters such as heart rate (HR), blood pressure (BP), and urine output are poor markers of fluid surplus, also implying that a patient's progressive fluid accumulation often eludes clinicians. Similarly, a state of hypovolemia is also commonly misdiagnosed by physicians, as studies have consistently shown that even when intravenous fluids are administered based on clinical judgment, only 50% of hemodynamically unstable patients actually respond to volume treatment (Fig.2)^{12,13}. Based on these considerations, to better direct fluid administration, Goal-Directed Fluid Therapy (GDFT), a strategy that uses dynamic hemodynamic variables, to better predict individual fluid needs and to circumvent the administration of an excessive volume, is being increasingly advocated in the perioperative setting^{14,15}.

Figure 2. Conceptual model illustrating relationship between time, volume of fluid, and potential complications

The model depicts a curvilinear association between time, volume of fluid, and morbidity. Insufficient volume of fluid early during illness is likely to lead to complications due to organ ischemia. In contrast, late administration of excess fluid after onset of organ dysfunction could potentiate organ edema. Optimal volume of fluid at any given time is likely to preserve organ viability without increasing morbidity.

2.1 Goal Directed Fluid Therapy

Goal Directed Fluid Therapy (GDFT) is a strategy that individualizes fluid management by tracking the response of dynamic indices of intravascular volume, such as cardiac output (CO), cardiac index (CI), stroke volume (SV), pulse pressure variation (PPV), and stroke volume variation (SVV), towards volume administration. GDFT has been mainly utilized to optimize fluid needs in surgical patients in the preoperative and intraoperative period, and in critically ill patients. When compared to static indicators of cardiac preload (such as right atrial pressure and pulmonary artery occlusion pressure), in the presence of a fluid challenge, changes in dynamic parameters have consistently been shown to better predict a further benefit from fluid therapy^{16,17}, and thus characterize patients who are “fluid-responders”.

When employed intraoperatively, early studies have shown that GDFT reduced morbidity and mortality mainly in high-moderate risk surgical patients¹⁴, with initial evidence suggesting a long-term survival benefit¹⁸; however, two recent randomized controlled trials found that

intraoperative GDFT was not beneficial, as low-risk patients treated with a more restrictive fluid regimen and within an ERP had morbidity and surgical recovery similar to those of patients treated with GDFT^{19,20}. This data were also confirmed by a recent meta-analysis²¹. The value of GDFT therefore seems to be more evident in high-risk patients, in patients undergoing major procedures with extensive fluid shifts^{4,14,22,23} and in patients treated without an ERP^{24,25}

Few studies have evaluated the benefits of continuing GDFT postoperatively in surgical patients, and these focus on patients admitted to High Dependency Units (HDUs) or ICUs. This data suggests that GDFT does reduce complications when employed for up to eight hours in postoperative cardiac and ICU patients²⁶⁻²⁸. Nevertheless, studies examining the potential for application of GDFT in the daily care of postoperative patients admitted on surgical wards are lacking. The first reason for this paucity of data is because surgical patients not admitted in HDUs or ICUs are commonly considered not at high-risk of developing postoperative complications, and therefore do not require advance hemodynamic monitoring. Secondly, measuring CO requires invasive or semi-invasive interventions that are not feasible on surgical wards.

2.2 Fluid Responsiveness

Patients in whom SV increases more than 10-15% after volume expansion are considered fluid responder (FRer). Theoretically, an increase in preload to an extent to obtain CO-values in the plateau of the Frank-Starling curve determines an optimal organ perfusion. Although being FRer does not necessarily mean being hypovolemic and it does not necessarily lead to tissue hypoperfusion, the association between fluid responsiveness (FR) and postoperative outcomes remains undetermined, especially in the postoperative period and in non-critically ill surgical patients.

2.3 Postoperative fluid therapy on surgical wards

In the postoperative setting, fluid administration has been shown to be non-uniform²⁹. In non-critically ill surgical patients intravenous fluids are commonly administered to hydrate and replace physiologic losses based mainly on clinical and inaccurate signs of hypovolemia. In the context of an ERP, early fluid intake is encouraged (at least 1.75 liters/day), and

intravenous fluids are discontinued soon after surgery and restarted only if clinically indicated^{30,31}, with the aim to maintain a zero fluid balance^{4,19}. Despite intravenous fluids are routinely administered in the postoperative period, the proportion of non-critically ill patients who are FRer after surgery is unknown. Moreover, preliminary data from a randomized controlled trial currently completed at our institution (NCT01818375) revealed that physicians considered necessary, based on clinical signs of hypovolemia, to restart or bolus intravenous fluids in 46.6% of patients admitted to surgical floors after colorectal surgery. As a result, almost half of the surgical population receives additional intravenous fluids without knowing the proportion of these patients in whom SV and CO significantly increase after such a volume expansion. Studies have consistently shown that when intravenous fluids are administered in critically ill patients based on clinical judgment (considering conventional signs of hypovolemia such as tachycardia, oliguria, hypotension and low central venous pressure), less than 50% of these patients are FRer (SV increases by at least 10-15% in response to VE)³². If this is also confirmed in surgical patients, administering fluids after surgery without tracking changes in CO and measuring FR might be potentially harmful by increasing the risk of fluid overload. This might either increase the risk of postoperative complications or further aggravate mild complications, and thereby delay surgical recovery.

3. CcNexfin CO-Trek technology

The ccNexfin system (BMEYE B.V. Amsterdam, the Netherlands, (Figure 1) is a non-invasive device that uses a finger cuff to measure continuous BP, and a pulse contour method to derive a beat-to-beat cardiac output³³. Initially adapted by the volume-clamp method using a finger cuff described by Peñáz in the 1970s³⁴, to derive BP, the finger cuff of the ccNexfin system dynamically applies a counter-pressure to keep a finger artery at a constant diameter (“clamped”) throughout a cardiac cycle. Changes in cuff pressure are measured by a photo-plethysmograph within the finger cuff. Using a proprietary algorithm including regular and automatic calibration (“Physiocal”), developed by Wesseling and co-workers³⁵, the system measures the point at which the artery “unloaded”, denoting a position in which the wall is under no tension, and the internal and external pressures are equal. This state represents the mean arterial pressure. The brachial pressure is then reconstructed from the finger pressure, in a manner previously validated by Guelen and colleagues³⁶. SV and subsequently CO may

then be derived, by dividing the systolic portion of the reconstructed brachial artery pressure curve by the aortic input impedance. To obtain this latter value, a 3-element Windkessel model previously described by Westerhof³⁷ is utilized, in addition to integration of pressure dependent, non-linear parameters to aortic impedance, such as age, gender, height, and weight, as previously described by Langewouters et al³⁸. Hemodynamic variables obtained using the ccNexfin CO-Trek technology have been validated in patients post cardiac surgery, by Bogert³⁹ and by Broch⁴⁰, who both alluded to the utility of the ccNexfin to apply GDFT in a non-invasive fashion. CcNexfin measurements have also been validated in ICU patients with decompensated heart failure⁴¹, which included hypotensive patients (systolic BP <90mmHg), patients in acute heart failure, and patients with atrial fibrillation. Other studies have further supported ccNexfin's ability to accurately track dynamic changes in CO⁴²⁻⁴⁴ and BP⁴³. Given its established ability to accurately measure dynamic SV and CO changes in a non-invasive manner, the ccNexfin system serves as an appropriate tool that might well enable the assessment of FR and guide fluid therapy in patients on a surgical ward and avoid potentially harmful fluid therapy in non fluid responders (Fig.3).

In 2014 a new version of noninvasive hemodynamic systems was introduced (ClearSight system). It upgrades the ccNexfin by providing up to 72 hours of hemodynamic insight using two cuffs on two fingers and it is integrated with a new platform (EV1000) that can be utilized with both noninvasive and minimally-invasive hemodynamic monitoring options.

Figure 3. ccNexfin device (BMEYE B.V. Amsterdam, the Netherlands), a non-invasive hemodynamic monitor, applicable to the middle phalanx of the 2nd, 3rd or 4th finger. Taken from Nexfin product information page.

Previously available at: <http://www.edwards.com/products/mininvasive/pages/ccnexfinsystem.aspx>.

Accessed 01 July, 2016.

Now found as ClearSight® at: <http://www.edwards.com/devices/Hemodynamic-Monitoring/clearsight>.

CHAPTER 2

PROSPECTIVE STUDY

1. Objectives

The aims of this study were to determine:

- 1) The incidence of FR in non-critically ill patients after major surgery
- 2) The incidence of FR after receiving a physician-ordered bolus of intravenous fluids based on clinical signs of hypovolemia
- 3) If a fluid challenge (FC) predicts FR in patients receiving a physician-ordered bolus of intravenous fluids
- 4) If FR is associated with and can predict postoperative complications and prolonged hospital stay

1.2 Study outcomes

Primary outcome:

- 1) The proportion of patients who are FRer in the first 48 h after surgery

Secondary outcomes

- 1) The incidence of FR after receiving a physician-ordered bolus of intravenous fluids based on clinical signs of hypovolemia
- 2) The ability of a fluid challenge (FC) to predict FR in patients receiving a physician-ordered bolus of intravenous fluid
- 3) The association between postoperative FR and 30-day complications and length of hospital stay

2. Materials and methods

2.1 Study population

Patients undergoing major elective abdominal, thoracic and esophageal surgery within an ERP at the Montreal General Hospital, and for whom postoperative intensive care unit was not requested.

2.2 Methodology

This was a prospective study including patients older than 18 years and above, undergoing major elective abdominal, thoracic and esophageal surgery, and treated with surgery-specific ERPs, first implemented in 2010 at the Montreal General Hospital for colorectal surgery⁴⁶, and subsequently developed at the same institution for thoracic⁴⁷ and esophageal surgery⁴⁸.

Patients' recruitment took place 2-4 weeks before surgery at the preoperative clinic of the Montreal General Hospital. Patients were informed about the study by their treating surgeon or by one member of the surgical team. If patients were interested to learn more about the study, they were approached by a research investigator not responsible for the care of the patient and invited to participate in the study. Those who accepted were provided with a more detailed explanation of the project, and consent was elicited.

Exclusion criteria:

1. age <18 years
2. emergency surgery
3. inability to read or communicate in either French or English
4. chronic kidney disease
5. congestive heart failure
6. severe aortic stenosis
7. patients not in sinus rhythm
8. patients requiring fluid restriction for any reason
9. known peripheral vascular disease or Raynaud's phenomenon
10. septic patients
11. acute circulatory shock

Preoperative risk was assessed and stratified by using the Charlson⁴⁹ and P-Possum score. Data collection was performed by one of the investigators of the research team. All data were reported in a data collection sheet, and all the information were kept confidential and housed in the REDcap secure database.

2.3 Perioperative care

2.3.1 Preoperative Period

As per usual practice, the ERP patient information resource provides directives for preoperative fasting and fluid intake. These patients are encouraged to drink up to two hours before hospital admission, and also receive preoperative carbohydrate drinks the night before (100 grams), and the morning of surgery (50 grams) when indicated^{30,31}. Additionally, routine use of full mechanical bowel preparation is avoided, and is prescribed only in selected cases (about one third of colorectal patients⁵⁰)

The patient's weight was obtained upon arrival in the operating room. Similarly, the use of mechanical bowel preparation, the use of preoperative carbohydrate drinks and duration of preoperative fasting was recorded.

2.3.2 Anesthetic and analgesic management

Anesthetic management and choice of postoperative analgesia were as per usual care, at the discretion of the staff anesthesiologist in-charge of the case. An arterial line or central venous line may have been inserted, and GDFT employed if deemed necessary.

2.3.3 Surgical management

Surgical approach was as per usual care, at the discretion of the staff surgeon. Usually minimally invasive approaches are used in about 75% of colorectal resections, 40% of esophageal resections and 15% of thoracic lobectomies.

2.3.4 Post-anesthesia Care Unit

On arrival to the Post-anesthesia Care Unit (PACU), basic hemodynamic parameters, including HR, BP, oxygen saturation, respiratory rate, temperature, and central venous pressure (CVP), if available, were recorded according to standardized PACU protocol. A research investigator collected then initial PACU values for these hemodynamic variables. Surgical time, estimated surgical blood loss, urine output, and intraoperative fluid and blood product administration were recorded. PACU care were dictated by the treating staff anesthesiologist. Patients were discharged from PACU according to standard institutional criteria.

2.3.5 Surgical floor

Postoperative care management, including the beginning of oral diet and fluid management, was conducted according to the ERP and treating surgical team. If required, VE (volume of the solution to be infused and type of the intravenous solution) was decided case by case by the surgical team. The patient's weight was obtained daily until hospital discharge using the same scale as preoperatively. Patients were typically discharged as per the ERP criteria (ie, afebrile, able to tolerate oral diet, pain is controlled (numeric rating scale (NRS) < 4), and able to ambulate).

2.4 Assessment of fluid responsiveness

The research investigator working in the department of Anesthesia assessed FR on two occasions:

- 1) Upon arrival to the PACU, and every day before breakfast during the first 48 h after surgery. FR was assessed by measuring SV and CO obtained by the ccNexfin system at base line and 1 minute and 5 minutes following 250 ml of Lactated Ringer's given as fluid challenge. A patient was considered a fluid responder if SV increased by at least 15% 1 minute or 5 minutes after the fluid challenge. A cut-off of 15% has been chosen as it represents the minimal clinical significant difference between two CO measurements obtained by thermodilution⁵¹. Daily assessment of FR, regardless of whether patients received intravenous fluids, determined the proportion of patients

who are FRer and if FR is associated with an increased risk of complications and/or prolonged hospital stay.

- 2) When a physician-ordered bolus of intravenous fluids was administered, either in PACU or on the surgical floor upon standard evaluation of hemodynamic parameters, urine output, surgical losses, and laboratory test abnormalities. FR was assessed by measuring SV and CO obtained by the ccNexfin system before the administration of the bolus and 1 minute and 5 minutes after the end of the infusion. A patient was considered FRer if SV increased by at least 15% 1 minute or 5 minutes after the end of the infusion.

2.5 Prediction of fluid responsiveness

A fluid challenge of 250 ml of Lactated Ringer's was used to predict FR before the administration of any physician-ordered bolus of intravenous fluids, either in PACU or on the surgical floor upon standard evaluation of hemodynamic parameters, urine output, surgical losses, and laboratory test abnormalities. A patient was considered FRer if SV increases by at least 15% 1 minute or 5 minutes after the end of the fluid challenge. The utilization of fluid challenges has been shown to have high-accuracy (Receiver Operating Characteristic (ROC) curve of > 0.9) to predict FR in spontaneously breathing patients before volume expansion is initiated⁵². Furthermore, administration of fluid challenges to predict FR has already been described in several trials, including those with sick patient populations⁵³ (ICU patients⁵⁴, patients undergoing major surgery⁵⁴, and patients with EF $<40\%$ ⁵⁴).

2.6 Measurement of FR

2.6.1 Daily assessment of FR after a FC

After surgery in PACU, and daily (before breakfast) for the first 48 h after surgery the research investigator administered a fluid challenge.

The research investigator also measured hemodynamic variables including HR and BP. CVP was measured in PACU if patients receive a central venous catheter. Then, the ccNexfin system was applied in a standardized fashion according to manufacturer recommendations⁵⁵:

an appropriately sized finger cuff was selected and placed around the patient's middle finger. The wrist unit and heart reference sensor (HRS) were then placed around the patient's wrist and ring finger respectively. The system was zeroed, and the sensor end of the HRS was placed at the level of the patient's heart, which allows for compensation for hydrostatic pressure differences between the finger and the heart. The ccNexfin then calculated and displayed baseline CO, CI, and SV-values. A fluid challenge of 250 ml of Lactated Ringer's solution (Baxter, Lactated Ringer's Injection, USP, 1000 mL VIAFLEX Plastic Container) was administered over 5 minutes. One minute following fluid challenge completion, the same hemodynamic values (as described above) were again recorded. An increase of SV by at least 15% 1 or 5 minute after the end of the fluid challenge was considered clinically significant, and the patient considered FRer (Fig.4).

Figure 4. Daily assessment of FR before breakfast. Fluid challenge: 250 ml Lactated Ringer's over 5 min. SV=Stroke Volume

2.6.2 Assessment of FR when a physician-ordered bolus of fluids is administered

Prior to administration of a non-emergent fluid bolus ordered by the treating physician, nurses additionally paged the research investigator who measured ccNexfin CO-parameters as described earlier and measure FR. For simplicity, a single pager number was used, and it was affixed to the front of the chart of patients included in the study. A copy of the study protocol was also given to nurses in the PACU and on the surgical floors for perusal.

The need for VE was evaluated by the anesthetist in charge in PACU, or by the surgical team on the surgical ward. Hemodynamic variables triggering fluid administration were decided based on standard evaluation of hemodynamic parameters, urine output, surgical losses and

laboratory test abnormalities. The total type and amount of intravenous solution used was decided by the anesthetist in charge or by the surgical team, taking into account that 250 cc Ringer's Lactate as fluid challenge was administered to predict FR as per study protocol.

Before VE, hemodynamic variables including HR and BP were measured by the research assistant. CVP was measured in PACU if patients receive a central venous catheter. The ccNexfin was applied as described above to calculate and displayed baseline CO, CI, and SV-values. One and 5 minutes after the end of the fluid bolus, the same hemodynamic parameters were measured again. An increase of SV by at least 15% 1 or 5 minute after the end of volume expansion was considered clinically significant, and the patient considered FRer. If any further bolus of fluid must have been administered, FR and basic hemodynamic variables were measured in the same manner (Fig.5), Appendix 1.

Figure 5. On call assessment of FR (6.30 AM-7.30 PM).

2.6.3 Prediction of FR before the administration of a physician-ordered bolus of intravenous fluids

A fluid challenge of 250 ml of Lactated Ringer's solution (Baxter, Lactated Ringer's Injection, USP, 1000 mL VIAFLEX Plastic Container) was administered over 5 minutes by the research investigator before volume expansion. One and 5 minutes following the end of the fluid challenge, basic hemodynamic values (as described above) as well as CO, CI, and SV obtained from the ccNexfin system, were again recorded. An increase of SV by at least 15% 1 minute or 5 minutes after the end of the fluid challenge was considered clinically significant. Upon termination of a fluid challenge, the decision on whether to proceed with volume expansion was taken by the treating physician based only on standard signs and measures of hypovolemia and not on any of the ccNexfin SV and CO measurements obtained during the fluid challenge (Figure 5). The proportion of patients identified as FRer after VE was compared with the proportion of patients responding to the fluid challenge.

The research investigator was available to measure FR when a physician-ordered bolus of intravenous fluids was administered from 6.30 AM to 7.30 PM every day during patient hospitalization. For patient safety, the research investigator had to arrive at the bedside within ten minutes of being paged, in order to measure FR before volume expansion. Intravenous fluids were administered without measuring CO and administering a fluid challenge if:

- a) the research investigator was not able to arrive at the bedside within ten minutes;
- b) the treating physician considered immediate administration of intravenous fluids necessary.

CO measurements were not taken before administering blood products, as blood products in surgical patients are either quickly administered to treat postoperative bleeding (inability to arrive in time at the bedside to determine fluid responsiveness) or slowly administered to correct coagulopathy or thrombocytopenia (therefore not considered as volume expansion). Blood products administration (erythrocytes, platelets, fresh frozen plasma, or cryoprecipitate) was also at the discretion of the staff anesthetist (in PACU) or at the discretion of the surgical team (surgical ward).

All ccNexfin values obtained before and after volume expansion and any fluid challenge were blinded to the treating anesthetist, the surgical team and the nursing team.

Because the lack of a standard definition of FR, it was decided to assess SV changes 1 min and 5 min after a FC or after VE. Moreover, to improve the accuracy of the hemodynamic measurements, we did not use an instant SV measurement, but the 1 min average of each hemodynamic variables, obtained before and after (1 min and 5 min) a FC or a VE.

2.7 Dynamic Arterial Elastance

Systemic arterial blood pressure is the result of the interaction between left ventricular ejection and the arterial system⁵⁶. For the same increase in CO, arterial blood pressure will change depending on baseline arterial tone⁵⁷. Therefore, the degree to which arterial blood pressure increases is a function of both left ventricular ejection and arterial elastance. Elastance is the change in pressure for a change in volume⁵⁸. In this regard, Cecconi *et al*⁵⁹ have shown that the functional assessment of arterial load by the dynamic arterial elastance

(Ea_{dyn}), defined as the ratio between pulse pressure variation (PPV) and stroke volume variation (SVV) during a single respiratory cycle, can be used as an index to predict the arterial blood pressure response to FC, in patients who are FRer⁵⁷. Therefore, the higher the Ea_{dyn} value, the more likely arterial blood pressure is to improve after an FC. In this study we evaluated the effectiveness of Ea_{dyn} for predicting the arterial blood pressure response to a FC in patients who were FRer patients. According to Cecconi *et al.* preinfusion Ea_{dyn} value >1.06 in FRer patients, predicted a positive MAP response ($MAP \geq 10\%$) after fluid administration with a sensitivity and specificity of 88.2% (approximate 95% CI, 64%–99%), respectively.

2.8 Outcome measures

- 1) Incidence of in hospital and 30-day postoperative complications. Postoperative complications were defined *a priori* (Appendix 2) and classified using the Clavien score⁶⁰. The Comprehensive Complication Index was also calculated (Appendix 3 and 4)
- 2) Assessment of FR: the proportion of patients who are at least one time FRer in the first 48 h after surgery or after a physician-ordered bolus of intravenous fluids
- 3) Prediction of FR: the probability of being FRer after a physician-ordered bolus of intravenous fluids was tested before initiating volume expansion by administering a fluid challenge of 250 ml of Lactated Ringer's
- 3) Indications triggering a physician-ordered bolus of intravenous fluids, amount and type of fluid administered, duration of the infusion
- 4) Ea_{dyn} : preinfusion PPV/SVV ratio of FRer patients calculated noninvasively with the ccNexfin®. Patients in whom MAP increased by $\geq 10\%$ were considered MAP responders.
- 5) Perioperative fluid balance: total amount and type of intraoperative and postoperative intravenous fluid and blood products administered, estimated surgical blood loss, intraoperative and postoperative urinary output, stoma, drainage and chest tube losses
- 6) Intraoperative and postoperative hemodynamic data: systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, CVP (in PACU, if available), oxygen saturation

- 7) Incidence of arterial hypotension, defined as systolic blood pressure less than 90 mmHg or less than 20% of the baseline value Number of patients (reported as percentage) requiring intraoperative and postoperative vasopressors in PACU and in ICU
- 8) Quality of surgical recovery quantified by the Qo-Recovery score, every day during hospital stay⁴⁵
- 9) Readiness to be discharge: achievement of discharge criteria as defined by each ERP
46-48
- 10) Length of hospital stay: effective time when patients leave the hospital

2.9 Data collection

Data collection was performed by the investigators of the research team. They collected hemodynamic measurements and assessed FR and the other postoperative outcomes, including postoperative complications. In-hospital complications were collected daily, and post-discharge complications, readmission rate and emergency department visits by reviewing medical records (including radiological and laboratory exams) 30 day after surgery; patients were not contacted after being discharged. All complications were reported in the study form and after in the study database. All the information was kept confidential.

2.10 Sample size and statistics

Approximately 600 patients per year undergo major colorectal, thoracic and esophageal surgery at the Montreal General Hospital. Assuming that 65% of the patients agree to participate in the study and among these 30% cannot be recruited because of exclusion criteria, 15% are excluded because require unexpected ICU admission, and 15% because of technical problems in measuring CO and SV, we estimated that in 1-year FR can be assessed in 160 patients undergoing major surgeries.

Data are presented as proportion, mean $\pm$ standard deviation, median and interquartile range and relative risk and 95% confidence interval when appropriate. Two-tailed student t-test (paired and unpaired when necessary) has been used to compare parametric data, and Mann-

Whitney U test to compare non-parametric data. Chi-square test (χ^2) has been used for the comparison of categorical variables. After adjusting for confounders (age, intraoperative estimated blood loss (>500 ml), intraoperative fluid balance (<1000 ml), duration of surgery, and negative fluid balance in the first 24 hours after surgery) a multiple logistic and linear regression has been used to assess the association between FR and postoperative complications and between FR and prolonged hospital stay, respectively. . Data were analyzed with SPSS statistic version 22 (IBM, New York, USA) and STATA 14. Nexfin CC data were extracted using Frame Inspector (Frame inspector software version 2.3.0.2, BMEYE BV, Amsterdam, the Netherlands) and analyzed using SPSS Statistics version 17.0 and STATA 14.

Data from the Nexfin monitor were exported for inspection to an Excel file using the FrameInspector software (version 2.3.0.2, BMEYE, Amsterdam, The Netherlands).

2.11 Potential risk and discomfort of the study

Fluid challenges are a widely accepted maneuver to determine FR, and no study using fluid challenges or GDFT has yet reported an increased incidence of adverse reaction⁶¹. Since patients had only received a daily supplement of 250 mL Lactated Ringer's solution, this study did not have significant risk. Furthermore, according to protocol and to help enhance patient safety, patients with co-morbidities placing them at increased risk for volume overload were excluded from this study.

The risks associated with the use of the ccNexfin are negligible. This device is completely non-invasive, and the probe is applied to the finger in a similar fashion to a pulse oximeter (Figure 1). It has been reported to be safe for finger microcirculation⁶², and no adverse event associated with its application has yet been described and has happened during our study.

2.12 Institutional review board and study registration

Institutional review board approval for the conduct of this study has been granted from the lead institution (14-452-SDR) and the study registered on ClinicalTrial.gov (NCT02418663).

3. Results

Overall, 195 patients were enrolled, 23 of whom were excluded from the analysis either because of withdrawal of consent ($n = 7$) or because of drop-outs (aborted surgeries, $n = 3$, immediate postoperative ICU, $n = 6$, technical difficulties with ccNexfin, $n = 7$) (Fig.6).

Figure 6. Consort Diagram.

FR was measured 551 times, in 172 patients. Patients' characteristics are reported in Table 1 and intraoperative data are shown in Table 2.

3.1 Fluid responsiveness: daily assessment after a FC

FR after a FC was present in 52 patients (30.2%) at least one time in the first 48 hours after surgery. There was a higher percentage of FRer immediately after surgery and during postoperative day 1: the proportions of responders were 15.2%, 16.2% and 12%, respectively, for each daily assessment in the first 48 hours. (Fig.7 and 8).

Figure 7. Incidence of FR after the delay FC in the first 48 h after surgery.

Figure 8. FRers after the delay FC. POD = postoperative day.

Demographic characteristics were similar among FRer and not FRer (Table 1). Intraoperative characteristics were also similar, except that FR was more present after esophageal surgery,

after larger blood losses and longer operations and FRer received a larger amount of fluids (Table 2).

	<i>All (n=172)</i>	<i>FRer (n= 52)</i>	<i>Not FRer (n= 120)</i>	<i>p-value</i>
<i>Age, years</i>	61.1 ± 11.1	62.2 ± 12.0	60.6	0.391
<i>Sex M/F, n</i>	91/81	29/23	62/5	0.621
<i>Weight, kg</i>	76.0 (64.0-87.8)	77.5 (57.4-90.5)	75.9 (65.2-86.9)	0.668
<i>BMI, kg/m²</i>	26.7 (23.3-30.2)	26.0 (21.7-30.4)	26.7 (23.6-30.2)	0.472
<i>ASA n (%)</i>				
<i>I</i>	8 (4.7)	4 (7.7)	4 (4.7)	0.212
<i>II</i>	117 (68.0)	31 (59.6)	86 (68)	0.120
<i>III</i>	47 (27.3)	17 (32.7)	30 (27.3)	0.298
<i>CR-POSSUM(%)</i>				
<i>Physiology</i>	15.5 (14-18)	16 (14-19)	15 (14-19)	0.188
<i>Operative</i>	15 .1 (14-16)	15 (14-17)	15 (14-17)	0.574
<i>Predictive Mortality</i>	1.7 (1.16-3.05)	1.9 (1.24-3.61)	1.49 (1.07-2.79)	0.147

Table 1. Demographic and preoperative characteristics of patients. Data are presented as means ± SD, medians (interquartile range) or as absolute numbers. M/F = Male/Female. ASA class = American Society of Anesthesiologists physical status classification.

	<i>All (n=172)</i>	<i>FRer (n= 52)</i>	<i>Not FRer (n= 120)</i>	<i>p-value</i>
<i>Type of Surgery, n (%)</i>				
<i>Abdominal</i>	69 (40.1)	20 (38.5)	49 (40.8)	0.771
<i>Thoracic</i>	81 (47.1)	19 (36.5)	62 (51.7)	0.068
<i>Esophageal</i>	22 (12.8)	13 (25.0)	9 (7.5)	0.002
<i>Type of Anesthesia, n (%)[†]</i>				
<i>Inhalational</i>	148 (86.0)	46 (88.5)	102 (85)	0.547
<i>TIVA</i>	22 (12.8)	5 (9.6)	17 (14.2)	0.412
<i>Type of Analgesia, n (%)^{††}</i>				
<i>PCA ± TAP block</i>	58 (33.7)	15 (28.8)	43 (35.8)	0.373
<i>Epidural</i>	104 (60.5)	35 (67.3)	69 (57.5)	0.227
<i>Others</i>	9 (5.2)	2 (3.8)	7 (5.8)	0.591
<i>Intravenous fluids (ml/kg/hr)[^]</i>	7.6 (5.0-10.7)	7.23 (4.1-10.7)	7.8 (3.5-10.9)	0.938
<i>Crystalloids (ml)</i>	1400 (1000-2000)	1500 (1.100-2075)	1125 (1000-2000)	0.019
<i>Colloids (ml)</i>	0 (0-0)	0 (0-0)	0 (0-0)	0.028
<i>Blood (ml)</i>	0 (0-0)	0 (0-0)	0 (0-0)	0.015
<i>Blood loss (ml)</i>	200 (50-300)	225 (100-500)	150 (50-300)	0.020
<i>Duration of surgery (min)</i>	168 (96-236)	203 (129-253)	142 (84-224)	0.005

Table 2. Intraoperative data.

[†] Data from 2 patients are missing. ^{††} Data from 1 patient are missing. [^] Data from 4 patients are missing.

TIVA=Total intravenous anesthesia, PCA= Patient controlled analgesia, TAP block= Transverse abdominis plane block.

3.2 Fluid responsiveness: *on call* assessment

VE was clinically deemed 72 times in 42 patients. In these cases, FR was assessed only 16 times (in 15 patients) out of 72 times (22.2%) because VE was requested during night-shift (32 times), patients refused a FC (6 times), nurses did not call the study investigator (17 times) or because there were technical problems with the ccNexfin (1 time). When FR was assessed, only 4 times (25%) patients were FRer after VE (Fig.9).

Figure 9. On call assessments of FR: individual changes in SV before and after VE. FR was present 4 times (marked in red). SV reported in ml.

Patient	VE Indication	VE (Type/Amount)	VE (Time, min)	FR_FC	FR_VE	Clinical problem solved ?	Postop Complications
1	Hypotension	VL 250 ml	12	✓	X	✓	X
2	Hypotension	VL 500 ml	12	X	X	X	✓
3	Hypotension	NS 1000 ml	43	X	X	X	✓
4	Hypotension	RL 500 ml	60	X	X	✓	X
5	Hypotension	RL 500 ml	10	X	X	✓	X
6	Hypotension	RL 1000 ml	60	X	X	X	✓
7	Hypotension	VL 500 ml	60	✓	✓	X	✓
8	Hypotension	RL 500 ml	30	X	✓	X	✓
8	Hypotension	NS 500 ml	120	X	X	✓	✓
9	Low urine output	NS 500 ml	60	X	X	X	X
10	Hypotension	VL 500 ml	25	X	✓	✓	✓
11	Hypotension	RL 250 ml	10	X	X	X	X
12	Hypotension	RL 250 ml	10	X	X	✓	X
13	Hypotension	VL 500 ml	20	X	✓	✓	✓
14	Hypotension	RL 500 ml	30	X	X	X	✓
15	Hypotension	RL 200 ml	10	X	X	X	✓

Table 3. VE in the 15 patients studied. VE = Volume Expansion, RL = Ringer Lactate, NS = Normal Saline, VL= Voluven ®, Hydroxyethyl starch (HES).

The indication triggering VE was mainly arterial hypotension, except one time, during which VE was required because of low urine output. Patients received either crystalloids or colloids, with a volume ranging from 250 ml to 1000 ml, administered between 12 minutes and 2 h. Only 43.7% of the times VE was able to correct the clinical problem triggering fluid administration (Table 3). Complications occurred in 60% of cases and were respiratory (55%), surgical (33%), other medical (anemia) (12%).

3.3 Regression analysis

Complications occurred in 53.8% of FRer and in 45% of non-FRer (p=0.719). FR was found to be associated with prolonged hospital stay (p=0.018). However it was not associated with an increased rate of postoperative complications (Relative Risk, $RR_{crude} = 1.19$, 95% Confidence Interval, CI=0.86 to 1.64, p-value=0.286; $RR_{adjusted} = 1.08$, 95%CI=0.68 to 1.70, p-value=0.719), admissions in ICU (p=0.320), severity of complications calculated with 30-day Clavien I-II (p=0.760), 30-day Clavien III-IV (p=0.677), 30-day CCI (p= 0.085), emergency department visits (p=1.000) and readmissions (p=0.993) within 30 days. (Table 4)

After controlling for confounders, FR was not an independent predictor of complications (Odds Ratio, $OR_{crude} = 1.16$ 95%CI=0.68 to 2.01, p-value=0.579; $OR_{adjusted} = 0.98$ 95%CI=0.42 to 2.26, p-value=0.965) and length of hospital stay (β -coefficient $_{crude} = 3.50$ 95%CI=1.01 to 6.00, p-value=0.006 β -coefficient $_{adjusted} = 1.50$ 95%CI=-1.32 to 5.56, p-value=0.225). (Table 5) Subgroup analysis in patients undergoing esophageal surgery did not show any statistically significant result (Table 6).

	FRer (n=52)	Not FRer (n=120)	RR _{crude} (95%CI)	p-value	RR _{adjusted} * (95%CI)	p-value
LOS, days*	5 (3-8)	4 (3-6)	-	0.018	-	-
Patients with at least one 30-day complications, n (%)	28 (53.8)	54 (45.0)	1.19 (0.86 to 1.64)	0.286	1.08 (0.68 to 1.70)	0.719
In-hospital	28 (53.8)	51 (42.5)	1.26 (0.91 to 1.75)	0.170	1.27 (0.78 to 2.08)	0.381
Respiratory	8 (15.4)	4 (3.3)	4.61 (1.45 to 14.65)	0.004	4.77 (0.91 to 25.1)	0.477
Infectious	2 (3.8)	6 (5.0)	0.77 (0.16 to 3.68)	0.741	0.22 (0.01 to 3.21)	1.000
Cardiovascular	5 (9.6)	6 (5.0)	1.92 (0.61 to 6.02)	0.256	3.92 (0.29 to 53.37)	0.333
Renal	2 (3.8)	0 (0.0)	-	0.031	-	-
Surgical	14 (26.9)	28 (23.3)	1.15 (0.66 to 2.00)	0.615	1.08 (0.50 to 2.32)	0.830
Other	11 (21.2)	21 (17.5)	1.34 (0.62 to 2.32)	0.572	1.23 (0.51 to 2.95)	0.751
Post-discharge, n (%)	4 (7.7)	9 (7.5)	1.07 (0.34 to 3.34)	1.000	0.57 (0.13 to 2.38)	0.999
Patients admitted to ICU, n (%)	8 (15.4)	6 (5.0)	3.07 (1.12 to 8.42)	0.022	1.46 (0.42 to 5.13)	0.320
30-day Clavien, n (%)						
I-II	15 (28.8)	45 (37.5)	0.77 (0.47 to 1.25)	0.274	0.86 (0.43 to 1.71)	0.760
III-V	13 (25.0)	11 (9.2)	2.72 (1.30 to 5.68)	0.006	1.70 (0.66 to 4.37)	0.677
30-day CCI	8.7 (0-32.5)	0 (0-12.2)	-	0.085	-	-
ED within 30 days†, n%	1 (2.1)	12 (10.3)	0.21 (0.02 to 1.55)	0.081	0.19 (0.02 to 1.93)	1.000
Readmissions within 30 days††, n (%)	3 (6.3)	10 (8.5)	0.73 (0.21 to 2.54)	0.619	0.42 (0.08 to 2.18)	0.993

Table 4. Postoperative length of Hospital Stay (LOS) and postoperative morbidity in Fluid Responder (FRer) and not Fluid Responder (not FRer) patients. CCI= Comprehensive Complication Index. RR=relative Risk. Values are reported as absolute n (%), median

(interquartile range), mean $\pm$ standard deviation. T-test, Mann-Whitney, χ^2 or Fisher exact test when appropriate; * missing data (1 patient), †missing data (7 patients), ††missing data (6 patients).

	Univariate analysis			Multivariate analysis		
	OR/Beta-coefficient	95% CI	p-value	OR/Beta-coefficient*	95% CI	p-value
30-day complications	1.16	0.68 to 2.01	0.579	0.98	0.42 to 2.26	0.965
In-hospital	1.17	0.67 to 2.01	0.579	1.39	0.60 to 3.26	0.443
Post-discharge	0.08	0.03 to 0.25	<0.001	0.45	0.11 to 1.79	0.255
In-hospital						
Respiratory	0.18	0.08 to 0.29	<0.001	2.57	0.66 to 9.95	0.171
Infectious	0.04	0.01 to 0.16	<0.001	0.41	0.07 to 2.39	0.325
Cardiovascular	0.10	0.04 to 0.26	0.000	2.28	0.47 to 11.17	0.308
Renal	-	-	-	-	-	-
Surgical	0.37	0.20 – 0.67	0.001	1.11	0.44 to 2.80	0.825
Other	0.27	0.14 – 0.52	<0.001	1.10	0.41 to 2.99	0.843
30-day Clavien-Dindo						
Minor (I-II)	0.40	0.22 to 0.74	0.003	0.60	0.25 to 1.43	0.251
Major (III-IV)	0.33	0.18 to 0.62	0.001	1.87	0.63 to 5.61	0.251
LOS, days**	3.50*	1.01 to 6.00	0.006	2.11	-1.32 to 5.56	0.225

Table 5. Fluid responsiveness as predictor of postoperative complications and length of hospital stay (LOS). OR= Odds Ratio. Linear regression LOS analysis was also adjusted for the presence of intrahospital complications.

	FRer (n=13)	Not FRer (n=9)	RRcrude (95%CI)	p-value
LOS, days	8 (7-21.5)	8 (7-21)	-	0.364
Patients with at least one 30-day complications, n (%)	9 (69.2)	8 (88.9)	0.77 (0.50 to 1.19)	0.279
In-hospital	9 (69.2)	6 (66.7)	1.03 (0.57 to 1.86)	0.899
Respiratory	5 (38.5)	2 (22.2)	1.73 (0.42 to 7.03)	0.421
Infectious	2 (15.4)	1 (11.1)	1.38 (0.14 to 13.07)	0.774
Cardiovascular	3 (23.1)	3 (33.3)	0.69 (0.17 to 2.68)	0.595
Renal	2 (15.4)	0 (0.0)	-	0.217
Surgical	5 (38.5)	2 (22.2)	1.73 (0.42 to 7.03)	0.421
Other	2 (15.4)	1 (11.1)	1.38 (0.14 to 13.07)	0.774
Post-discharge, n (%)				
Patients admitted to ICU, n (%)	5 (38.5)	3 (33.3)	1.15 (0.36 to 3.65)	0.806
30-day Clavien, n (%)				
I-II	2 (15.4)	3 (33.3)	0.46 (0.09 to 2.22)	0.323
III-V	7 (53.8)	5 (55.6)	0.96 (0.44 to 2.09)	0.937
30-day CCI	32.4 $\pm$ 28.4	31 $\pm$ 15.4	-	0.897
ED within 30 days†, n%	0	1 (16.7)	-	0.205
Readmissions within 30 days††, n (%)	1 (11.1)	1 (16.7)	0.66 (0.05 to 8.72)	0.756

Table 6. Postoperative length of Hospital Stay (LOS) and postoperative morbidity in Fluid Responder (FRer) and not Fluid Responder (not FRer) in patients who underwent esophageal surgery. CCI= Comprehensive Complication Index. RR=relative Risk. Values are reported as absolute n (%), median (interquartile range), mean $\pm$ standard deviation. T-test, Mann-Whitney, χ^2 or Fisher exact test when appropriate; [†]missing data (1 patient), ^{††}missing data (1 patient).

3.4 Discriminative power of a Fluid Challenge in predicting FR before VE

The area under the receiver operating characteristic curve (ROC) of FC was 0.583 for predicting fluid responsiveness 1 minute or 5 minutes after volume expansion (Fig.10). The sensitivity and specificity of a FC was 0.25 and 0.91, respectively.

Figure 10. ROC curve for predicting FR after VE by administering a FC and measuring SV changes 1 minute or 5 minutes after the FC.

A (FR assessed 1 minute after FC and VE)

B (FR assessed 5 minutes after FC and VE)

Figure 11. ROC curve for predicting FR after VE by administering a FC and considering SV changes individually after 1 minute (A) or 5 minutes (B) after FC and VE.

By considering SV measures individually, before and after 1 or 5 minutes after administering the FC and after the VE we obtained 2 different ROC curves (Fig.11): in the first case the area under the ROC curve (SV changes measured 1 minute after administering the FC) was 0.423 for predicting fluid responsiveness after VE (SV changes measured 1 minute after VE), with a sensitivity of 0 and a specificity of 0.85; in the second case the area under the ROC curve (SV changes measured 5 minutes after administering the FC) was 0.667, with a sensitivity of 0.33 and a specificity of 1 (SV changes measured 5 minute after VE).

3.5 Dynamic arterial elastance ($E_{a_{dyn}}$)

Baseline $E_{a_{dyn}}$ was not significantly different ($p=0.853$) between MAP – responders and MAP – nonresponders (Fig. 12).

Figure 12. Baseline dynamic elastance ($E_{a_{dyn}}$) in FR patients. Distribution of $E_{a_{dyn}}$ values at preinfusion time according to mean arterial blood pressure (MAP) response to FC. Individual values of $E_{a_{dyn}}$ before FC in MAP-responders (MAP-R= MAP increase by $\geq 10\%$) and nonresponders (MAP-NR= MAP increase by $<10\%$) measured 1 or 5 min after the FC. Dashed line represents the optimal cutoff for dynamic arterial elastance ($E_{a_{dyn}}$) corresponding to 1.06⁵⁹. $E_{a_{dyn}} = PPV/SVV$. MAP Responder: MAP increase by $\geq 10\%$. PPV = Pulse Pressure Variation. SVV= Stroke Volume Variation. Missing data from 2 patients.

4 Discussion

The results of this study indicate that postoperative FR after a FC is present in 30.2% of non-critically ill patients undergoing major surgery at least one time during the first 48 hours after surgery (daily assessment). FR is not associated with complications and it does not predict a higher rate of complications or longer hospital stay. These data also showed that after VE expansion based on clinical signs of hypovolemia (*on call* assessment), only 25% SV significantly increases. Since this was the first clinical trial to assess and report FR in non-critically ill patients these preliminary results are not comparable to or supported by other findings.

Although almost one third of non-critically ill patients are FRer in the postoperative period, this condition was not associated with higher morbidity, supporting the hypothesis that being FRer doesn't necessarily mean being hypovolemic. In fact, this suggests that pre-emptive SV optimization based on the presence of FR, rather than SV optimization when clinically needed, might erroneously lead physician to administered fluids when fluids are not needed.

VE after surgery occurred only in 24.4% of patients a proportion significantly lower than what it was found in surgical patients treated with an ERP. Infact institutional data showed that 46.6% of colorectal patients admitted on surgical wards required a bolus of intravenous fluids (VE) after surgery (Baldini *et al.* unpublished data). It might have occurred that the surgical personnel who was aware about the rational and hypothesis of the study was more careful in deciding when administering additional intravenous fluids. However, patients were FRers only 4 times after VE (25% of times), meaning that only 25% of the times when patients received a bolus of intravenous fluids SV significantly increased. Although *on call* FR was measured a limited number of times, the incidence of FR was even lower than those reported in sicker patients admitted in ICU. Furthermore, the clinical problem triggering VE (hypotension 94% of the times) was solved in only 43.7% of the cases. This confirms that, deciding of administering fluids in non-critically ill patients based only on inaccurate signs of hypovolemia rarely increase SV and might be instead potentially harmful. In fact, Chappell *et al.*, showed that administering intravenous fluids without objective evidence of hypovolemia can be potentially dangerous as it determines an increase of the endothelial permeability, by

shedding the endothelial glycocalyx⁵, thus facilitating further fluid shift in the interstitial space and further loss of the intravascular volume.

It was found that the discriminative power of a FC in predicting FR before VE is not so accurate as previously reported, probably because of the small number of observations. SV measured 5 minutes after administering a FC seems to better predict FR 5 minutes after VE.

We also investigated the discriminative power of pre-infusion $E_{a_{dyn}}$ values to predict the pressure response after a fluid challenge in patients who were FRer⁵⁹. It was found that, at baseline, $E_{a_{dy}}$ was not significantly different between MAP-responders and MAP-nonresponders. This is in contrast with what was previously demonstrated in critically ill patients. In fact, although patients might benefit from the administration of a bolus of fluids, as SV might significantly increase after fluid administration, the pressure response to a bolus of fluid in FRer patients depends also on the arterial tone. This explains why despite SV significantly increases after a bolus of fluids patients with a low pre-infusion arterial tone (low $E_{a_{dyn}}$) still remain hypotensive. In this regard, the assessment of $E_{a_{dyn}}$ could help to discriminate those preload-dependent patients in whom arterial blood pressure will improve only with fluids or also by using vasopressors.

5 Limitations

In this study hemodynamic variables were derived noninvasively using the volume clamp method. Nexfin cardiac index values have proven to be unreliable in studies performed in critically ill patients, as they frequently receive vasoactive agents and are peripherally hypoperfused as most of them are in septic shock, or with cardiac stunning⁶³⁻⁶⁵. Bubenek et al.⁶⁶ concluded that the Nexfin device has limited accuracy compared with CO measured with the pulmonary artery catheter, although it is able to reliably track cardiac output changes after inducing preload modifying actions in a post-cardiosurgical population. However, this study was performed in a surgical population with normal peripheral perfusion and not receiving vasoactive agents, and previous reports have shown a good level of agreement with thermodilution cardiac output measurements or transthoracic or esophageal Doppler cardiac index in this population^{39,43,67,68}.

Finally, our study had a relatively low number of assessments on call. In that case FR was assessed only 16 out of 72 times (22.2%), which limited the generalizability of these preliminary results.

6. Conclusions

Thirty percent of non-critically ill surgical patients are FRers after surgery. After controlling for confounders, FR is not associated, and it does not predict postoperative complications. Similarly, it does not predict prolonged length of hospital stay. Fluid boluses administered only on the basis of clinical signs of hypovolemia rarely determine a significant increase of SV and might be potentially harmful. Specifically, administering intravenous fluids when not necessary and without objective measures of hypovolemia might increase the risk of fluid overload and complications.

While significant attention is paid to the optimization of fluid management in the operating room, there is still relatively little evidence available to guide clinicians on postoperative fluid management. Considering that boluses of intravenous fluids are administered on the basis of inaccurate measures of hypovolemia, identifying surgical patients admitted on surgical wards who do not benefit from this intervention might reduce morbidity and hospital stay and improve surgical recovery. Based on these preliminary results, further studies, including co-effectiveness analysis, are needed to determine whether postoperative fluid management employing FR measurements before VE might improve outcomes.

Study timeline
(6.30 AM-7.30 PM, Monday to Sunday)

On call assessment of Fluid responsiveness (FR)

Appendix 1. Assessment of Fluid Responsiveness (FR). Original study timeline distributed on the floor and in PACU. CO= Cardiac Output; FC = Fluid Challenge; VE= Volume Expansion; IV =Intravenous. During CO measurements epidural and intravenous fluids infusion rates will not be modified. Similarly, vasopressors will not be administered until VE is concluded.

Appendix 2: Definition of complications

DEFINITIONS OF INTRA- AND POSTOPERATIVE COMPLICATIONS

INTRAOPERATIVE

- *Clinically significant hemorrhage*: bleeding requiring intraoperative transfusion of packed red blood cells (PRBC)
- *Bowel injury*: injury of the small or large bowel requiring intraoperative repair or additional resection
- *Urinary tract injury*: injury of the ureter or bladder requiring intraoperative repair
- *Vascular injury*: injury of any major vessel (e.g. iliac artery or vein) requiring intraoperative repair
- *Cardiac or respiratory complications*: any cardiovascular (e.g. cardiac arrhythmia, myocardial infarction) or respiratory (e.g. pneumothorax) complication occurring during surgery.
- *Aspiration of gastric content*: intraoperative pulmonary aspiration of gastric content
- *Other*: any intraoperative injury to other viscera (e.g. spleen, vagina)

MEDICAL

Cardiovascular

- *Heart failure*: clinical or radiological signs of congestive heart failure and specific treatment initiated.
- *Myocardial infarction*: increase in cardiac enzymes or ECG changes.
- *Cardiac arrhythmia*: ECG confirmation of new arrhythmia requiring at least a pharmacologic intervention.
- *Cardiac arrest*: CPR performed.
- *Deep vein thrombosis*: radiological confirmation of deep vein thrombosis or anticoagulation started due to clinical findings
- *Pulmonary embolism*: radiological evidence of pulmonary embolism
- *Cerebrovascular accident*: new and persistent (>24 hrs) neurological deficit.

Respiratory

- *Pneumonia*: abnormal chest radiograph with signs of infection and initiation of antibiotic treatment.
- *Lobar atelectasis*: radiogram confirmation of at least one lobar collapse
- *Pleural fluid*: pleural effusion requiring drainage of the pleural cavity
- *Respiratory failure*: delayed extubation > 24 hours after primary surgery, or reintubation at any time for ventilatory support.

Infectious

- *UTI*: positive urine culture + upper or lower urinary symptoms unrelated to bladder catheter.
- *Wound infection*: opening of wound spontaneously or bedside or surgical debridement with clinical signs of infection (drainage of purulent material). Not included if part of intra-peritoneal abscess.
- *Intra- or retroperitoneal abscess*: Radiologic finding associated with systemic signs of infection or finding during reoperation.
- *Sepsis*: at least two SIRS criteria. Temperature < 36 or >38, pulse >90, respiratory frequency >20, leukocytosis (WBC>12) or leukopenia (WBC<4) AND documented or suspected infection.
- *Other infectious complications*: any other documented infectious complication (e.g. Clostridium difficile colitis)

Other medical

- *Acute Kidney Injury*: increase in serum creatinine $\times 2$ from baseline OR initiation of any form of peritoneal dialysis or hemodialysis.
- *Urinary retention*: Reinsertion of bladder catheter or inability to remove it before discharge excluding patients with chronic need of urinary drainage
- *Anemia*: low serum hemoglobin requiring transfusion of PRBC, unrelated to any identified source of bleeding
- *Hepatic dysfunction*: Increased serum bilirubin concentration > 34 $\mu\text{mol/l}$ (2 mg/dl) compared to preoperative value AND elevated liver enzymes AND has NOT undergone a pancreaticobiliary procedure.

- *Pancreatitis*: clinical signs and increase in serum amylase (x3 normal value) NOT secondary to ERCP procedure or other pancreatobiliary procedure
- *Other gastrointestinal complications*: any other complication of the gastrointestinal tract requiring treatment (e.g. diarrhea).
- *Psychiatric complications*: new psychiatric symptoms including delirium and depression, requiring pharmacological treatment.

SURGICAL

- *Anastomotic leak*: documentation at reoperation OR documentation by imaging technique (e.g. radiologically, endoscopically) of leakage from the surgical connection between the two bowel ends into the abdomen or pelvis with either spillage and/or fluid collection around the anastomotic site or extravasation through a wound, drain site, or anus.
- *Air leak*: any extrusion of air from normal gas-filled cavities including the upper airway, tracheobronchial tree, and gastrointestinal (GI) tract.
- *Bowel perforation*: documentation at reoperation OR radiologically of perforation of small or large bowel.
- *Mechanical bowel obstruction*: documentation at reoperation OR radiologically of mechanical small or large bowel obstruction.
- *Wound dehiscence*: separation of the abdominal wall muscle fascia large enough to necessitate operative closure of the wound OR incisional hernia diagnosed after primary discharge.
- *Bleeding*: any postoperative bleeding (e.g. intra-abdominal, gastrointestinal) requiring transfusion of at least 2 PRBC during surgery.
- *Primary postoperative ileus delaying discharge*: abdominal distention OR vomiting associated with intolerance of solid food intake beyond POD3 unrelated to any other ongoing complication.
- *Other surgical complications*: any other surgical complication necessitating treatment or delaying discharge (e.g. abdominal wall hematoma, blood per rectum)

ANESTHESIA RELATED

- *Post-dural puncture headache*: persistent headache requiring immobilization, related to puncture of the dura mater during epidural catheter placement
- *Epidural hematoma or abscess*: radiologically confirmed epidural hematoma or abscess

Symptoms delaying discharge (unrelated to any aforementioned complication, and requiring pharmacological treatment).

- *High stoma output*
- *Pain*

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications) [†] requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

[†] brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info

Appendix 3: Classification of surgical complications⁶⁰.

Taken from: Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibanes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of surgery* 2009; 250: 187-96.

Patient	Complications	Grade of Complication	Weights (MRV _{phys} × MRV _{pat})	CCI
A. Single complication				
Patient 1	Nausea and vomiting	I	300 (15 × 20)	8.7
Patient 2	Pneumonia	II	1750 (35 × 50)	20.9
Patient 3	Pneumothorax	IIIa	2750 (50 × 55)	26.2
Patient 4	Fascia dehiscence	IIIb	4550 (65 × 70)	33.7
Patient 5	Acute renal failure	IVa	7200 (80 × 90)	42.4
Patient 6	Anastomotic insufficiency	IVb	8550 (90 × 95)	46.2
B. Multiple complications				
Patient 7	Pain exacerbation	I	300	17.3
	Nausea and vomiting	I	300	
	Hematoma	I	300	
	Generalized edema	I	300	
Patient 8	Nausea and vomiting	I	300	30.8
	Pneumonia	II	1750	
	Urinary tract infection	II	1750	
Patient 9	Wound infection	I	300	40.5
	Urinary tract infection	II	1750	
	Gastric ulcer	II	1750	
	Pneumothorax	IIIa	2750	
Patient 10	Pneumonia	II	1750	56.1
	Arterial hypertension	II	1750	
	Anastomotic insufficiency	IIIb	4550	
	Gastric ulcer perforation	IIIb	4550	
Patient 11	Wound infection	I	300	88.6
	Urinary tract infection	II	1750	
	Deep venous thrombosis	II	1750	
	Gastric ulcer bleeding	IIIa	2750	
	Pleura empyema	IIIb	4550	
	Anastomotic insufficiency	IIIb	4550	
	Stroke	IVa	7200	
	Central line infection with septic shock	IVb	8550	
Example of the CCI calculated for patient 9: CCI = $\sqrt{(300 + 1750 + 1750 + 2750)/2} = 40.5$. Death is arbitrarily defined with a CCI of 100. ARDS indicates adult respiratory distress syndrome.				

Appendix 4: Examples of the Comprehensive Complication Index in Case of Single and Multiple Complications. Taken from Slankamenac K, Graf R, Barkun J., Puhan MA, Clavien PA: The Comprehensive Complication Index. A Novel Continuous Scale to Measure Surgical Morbidity. *Annals of Surgery* 2013;258: 1–7⁶⁹.

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