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Staggered Passive Leg Raising Test for predicting several degrees of fluid responsiveness in mechanical ventilated patients.

An observational study

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INDEX

1. ABBREVIATIONS.....	5
2. ABSTRACT.....	6
3. INTRODUCTION	7
3.1 FLUID THERAPY.....	7
3.2 UNDERSTANDING FLUID RESPONSSIVENESS	9
3.2.1 FRANK-STARLING PRINCIPLE	10
3.2.2 HEARTH-LUNG INTERACTIONS DURING MECHANICAL VENTILATION	11
3.3 INDICATORS OF FLUID RESPONSSIVENESS.....	12
3.3.1 STATIC INDICATORS OF FLUID RESPONSSIVENESS.....	13
3.3.1 DINAMIC INDICATORS OF FLUID RESPONSSIVENESS	15
3.4 FLUID RESPONSSIVENESS IN CLINICAL PRACTICE.....	18
3.4.1 PASSIVE LEG RAISING TEST.....	18
3.4.2 VIGILEO/FLOTRAC SYSTEM.....	20
3.4.3 OTHER TECHNIQUES.....	21
4. JUSTIFICATION.....	23
5. HYPOTHESIS	24
6. OBJECTIVES.....	24
6.1 MAIN OBJECTIVE	24
6.2 SECONDARY OBJECTIVES.....	24
7. METHODS.....	25
7.1 STUDY DESIGN.....	25
7.2 PARTICIPANTS	25
7.2.1 INCLUSION CRITERIA	25
7.2.2 EXCLUSION CRITERIA.....	25

7.3	SAMPLE.....	27
7.3.1	Sample size.....	27
7.3.2	Sample selection	27
8.	VARIABLES AND MEASUREMENTS.....	28
9.	DATA COLLECTION AND STUDY CIRCUIT	29
10.	STATISTICAL ANALYSIS	31
11.	WORK PLAN AND CHRONOGRAM	32
12.	BUDGET AND FEASIBILITY	34
13.	STRENGTHS AND LIMITATIONS.....	35
14.	IMPACT OF THE STUDY.....	36
15.	ETHICAL CONSIDERATIONS.....	37
16.	BIBLIOGRAPHY.....	39
17.	ANNEXES	43
17.1	ANNEX 1: CASE-REPORT FORM	43
17.2	ANNEX 2: VIGILEO/FLOTRAC SYSTEM	44
17.3	ANNEX 3: INFORMED CONSENT SHEET	46
17.4	ANNEX 4: PATIENT INFORMATION SHEET.....	47
17.5	ANNEX 5: RESEARCHERS COMMITMENT	48

1. ABBREVIATIONS

SV Stroke Volume

HR Heart rate

CO Cardiac output

MSP Mean systemic pressure

RAP Right atrial pressure

LV Left ventricle

RV Right ventricle

CVP Central venous pressure

GEDV global end diastolic volume

SVV Stroke volume variation

SV Stroke volume

PPV Pulse pressure variation

TV Tidal volume

RR Respiratory rate

PEEP Positive end expiratory pressure

IH Intraabdominal hypertension

PVR peripheral vascular resistance

ICU Intensive care units

PLR Passive leg raising test

SPLR Staggered passive leg raising test

Sat O₂ Oxygen saturation

EEO end expiratory occlusion

MAP Mean arterial pressure

OIT orotracheal intubation

2. ABSTRACT

STAGGERED PASSIVE LEG RAISING TEST TO PREDICT FLUID RESPONSIVENESS IN MECHANICAL VENTILATED PATIENTS.

Introduction: Fluid therapy is one of the cornerstones of resuscitation, although only 50% of critically ill patients are fluid responders. In recent years, the most traditionally used techniques to understand patient's fluid status, such as central venous pressure (CVP) or mean arterial pressure (MAP), have shown to be unreliable in predicting fluid responsiveness. Consequently, new techniques have been developed as improved predictors, such as, stroke volume variation (SVV) or continuous cardiac output (CO) monitoring systems.

FloTrac/Vigileo system calculates continuous CO and SVV by analyzing the arterial pulse waveform through semi-invasive arterial catheterization.

Passive leg raising (PLR) test is an alternative preload-modifying maneuver: when inferior limbs are raised an amount of blood is *autotransfused* to the central circulation. PLR has been included in several guidelines in critically ill patient's resuscitation. Combined with a SVV and CO monitoring system, PLR may help predict fluid responsiveness in critically ill patients.

However, none of these techniques have been proved to predict several degrees of fluid responsiveness, which could lead to a better and more individualized fluid therapy, where patients would receive the amount of fluid that their heart can manage.

Objectives: The aim of this study is to evaluate if Staggered Passive Leg Raising (SPLR) test can trigger significant changes on SVV, CO and MAP assessed by Vigileo/FloTrac device in mechanical ventilated patients in order to establish several degrees of fluid responsiveness.

Design: This is an observational, cross-sectional study performed in The department of Anesthesiology in a third level teaching facility, Hospital Universitari Josep Trueta. The study will be performed in 2017.

Participants and methods: Patients (n=32) attending the operating room between April and May 2017 for a major surgery who will need monitoring with Vigileo/FloTrac device, CVP and mechanical ventilation.

Measurements of SVV, CO and MAP will be obtained with Vigileo/FloTrac in baseline status, during SPLR test and after a fluid bolus. ANOVA analysis for repeated measures will be used for analyzing mean SVV, CO and MAP.

Key words: Fluid responsiveness, Vigileo/FloTrac, Passive leg raising (PLR), stroke volume variation (SVV), Cardiac output (CO)

3. INTRODUCTION

3.1 FLUID THERAPY

The cornerstone of resuscitation of hemodynamic unstable critically ill patients is often considered to be fluid loading (1). The need of fluid is a common situation in critical care and postsurgical patients and it may be a consequence of hormonal response to surgical stress (2), blood loss, maintenance of postsurgical fluid therapy, gastrointestinal or urinary loss, fluid redistribution, insensible loss due to the exposure in the surgical camp (2), burns or fever (3). Moreover, the surgical patient can present hemodynamic changes secondary to vasodilatation of the anesthetic drugs and neuroaxial block (2,4), and the surgical position or pressure on some cavities of the body during the surgery, as in laparotomy (5). All these situations can develop a functional or organic fluid depletion (6).

The aim of the fluid treatment is to ensure an adequate tissue perfusion including the damaged tissue to help wounds healing (2), by increasing cardiac output and oxygen delivery (7) but avoiding fluid therapy complication. Fluid balance near to zero is capable of reducing the postoperative complications in a dose-response relation, especially the cardiopulmonary complications(8). Consequences of fluid overload may be systemic, the pooling in the interstitium can lead to tissue edema affecting gut motility predisposing to postoperative ileus (9), lung and tissue edema (10), exerting hydrostatic pressure on microvasculature and difficulting tissue perfusion and oxygenation, and also impair wound healing predisposing to wound infection and dehiscence (11).

There are several situations in whose fluid therapy is indicated: resuscitation of a critical ill patient, routine maintenance, reposition of fluid loose and redistribution of fluid, moreover the reassessment of the indication of the treatment is very important (3).

Both, hypervolemia and hypovolemia are harmful states and attempts have to be made to administer the treatment in consonance with the patient status (12). Fluid therapy needs to be

seen as a treatment, evaluating its pros and cons, trying to avoid overdose or underdose in order to avoid collateral effects (7).

In critical ill patients, fluid overload can prolong mechanical ventilation and increase mortality of critically ill patients in general, but specially in patients with sepsis (13–15), acute respiratory distress syndrome (16–18), intra-abdominal hypertension (19) and acute kidney injury (20,2). Rivers et al. demonstrated in a study that a protocol of early goal-directed therapy reduces organ failure and improves survival in patients with severe sepsis and septic shock (17).

Little evidence is available for the type and exact dosing of fluid administration (1,3). The resuscitation of the critically ill patient requires an accurate assessment of the patient's intravascular volume status and the likelihood that the patient will respond to a fluid challenge. So indeed, resuscitation depends on volume responsiveness, or what is the same, it depends on the cardiac preload and the increase in stroke volume after starting the fluid therapy (22).

3.2 UNDERSTANDING FLUID RESPONSIVENESS

The main objective of cardiorespiratory system is to ensure tissue oxygenation, and the arrival of oxygen depends on cardiac output (CO) and arterial content of O₂. When assessing a patient in a critical situation, it is very important to keep in mind figure 1 scheme, because a correct oxygenation is crucial for his/her prognosis.

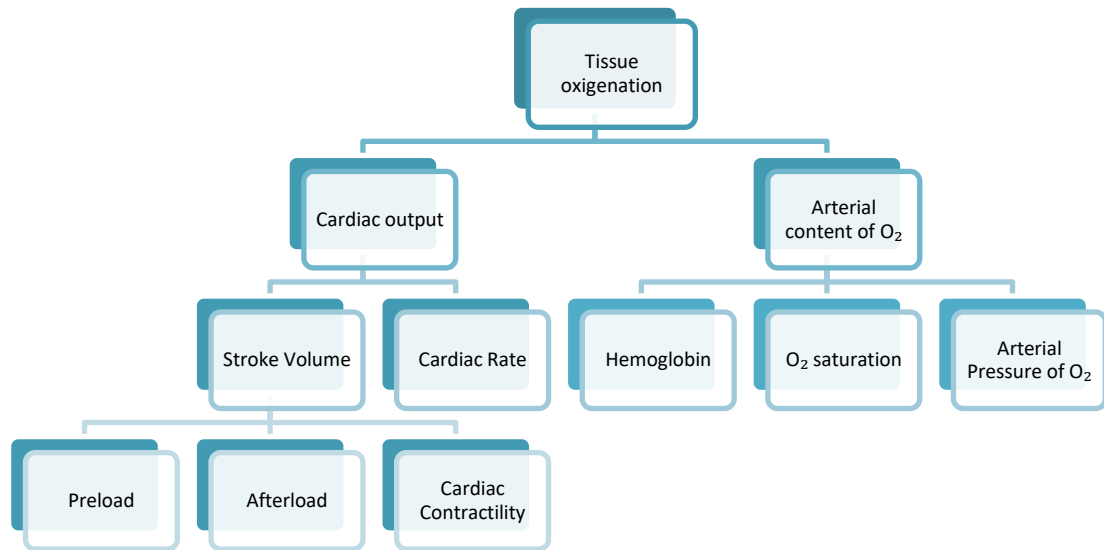


Figure 1. Determinants of tissue oxygenation (23).

One of the difficulties of fluid treatment is based on the different response to fluids, studies on different patients populations have demonstrated that only 50% of the patients are fluid responders (1,24–26). Thus when tissue hypoperfusion is likely, it is key to find out the patient’s position on the cardiac performance curve or Frank Starling curve to predict whether an increase in CO or SV is to be expected from fluid loading (1)

CO is the product of stroke volume (SV) and heart rate (HR) (23,27), and it is an extremely important cardiovascular variable that is continuously adjusted so that the cardiovascular system operates to meet the body transport needs. In turn, SV is determined by preload, afterload and cardiac contractility, as Frank Starling’s law states(7,22,23,27,28).

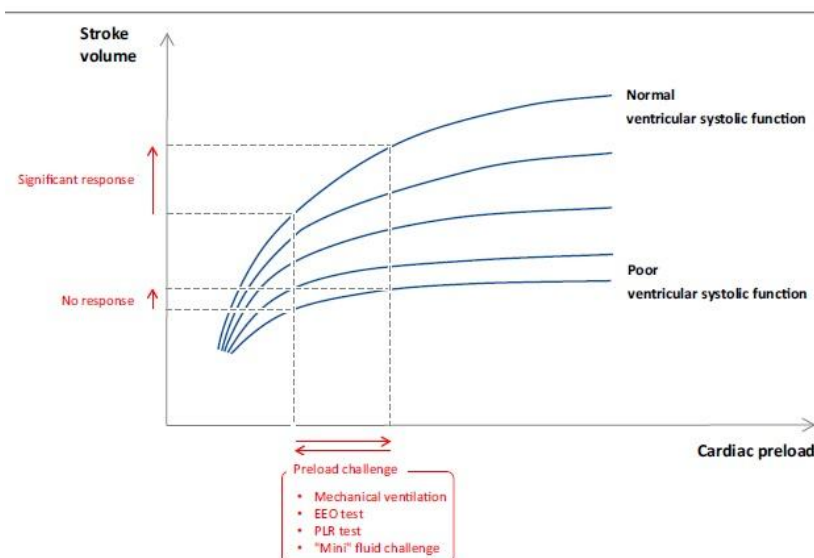
Besides, preload depends on venous return (VR), which is defined by mean systemic pressure (MSP), vascular resistance and right atrial pressure (RAP):

$$VR = \frac{MSP - RAP}{\text{Vascular resistance}} \quad (28);$$

meaning that venous return can be increased by fluid loading (1). However, if this increase in venous return can produce an increase in SV depends, inter alia, on heart contractility. For example, it has been studied that non-volume responsive patients do not increase their CO presumably because the increase in arterial pressure-induced left ventricular afterload was a more important determinant of CO than was the increase in MSP (29).

3.2.1 FRANK-STARLING PRINCIPLE

According to Frank-Starling principle, as the preload increases, left ventricular stroke volume increases until the optimal preload is achieved at which point the stroke volume remains relatively constant. Once the left ventricle is functioning near the “flat” part of the curve, fluid loading has little effect on the stroke volume (22). The shape of the Frank Starling curve is dependent on other factors influencing cardiac function besides preload, most notably contractility and afterload (1). Thus, varying shapes in the Frank-Starling curve can lead to different cardiac response depending on ventricular systolic function. (7) (Figure 2)



In normal physiological conditions, both ventricles operate on the ascending portion of the Frank-Starling curve, and this mechanism provides a functional reserve to the hearth in situations of acute stress (22)

Cardiac function does not

Figure 2 Frank-Starling relationship (7)

depend directly and solely on the cardiac preload and consequently it does not help in predicting fluid responsiveness, however an increase in stroke volume and cardiac output as ventricular systolic function indicators can predict fluid responsiveness (7).

3.2.2 HEARTH-LUNG INTERACTIONS DURING MECHANICAL VENTILATION

Mechanical insufflations decrease preload and increase afterload of the right ventricle (RV) due to the decrease in the venous return pressure gradient and to the inspiratory increase in transpulmonary pressure (22). Both, lead to a reduction in RV stroke volume.

The inspiratory reduction in RV ejection leads to a decrease in left ventricle (LV) filling, thus the LV preload reduction may induce a decrease in LV stroke volume. The cyclic changes in RV and LV stroke volume are greater when the ventricles operate on the steep rather than the flat portion of the Frank-Starling curve (Figure 3) (22). The magnitude of the respiratory changes in LV stroke volume assessed as stroke volume variation (SVV) is an indicator of biventricular preload dependence (22).

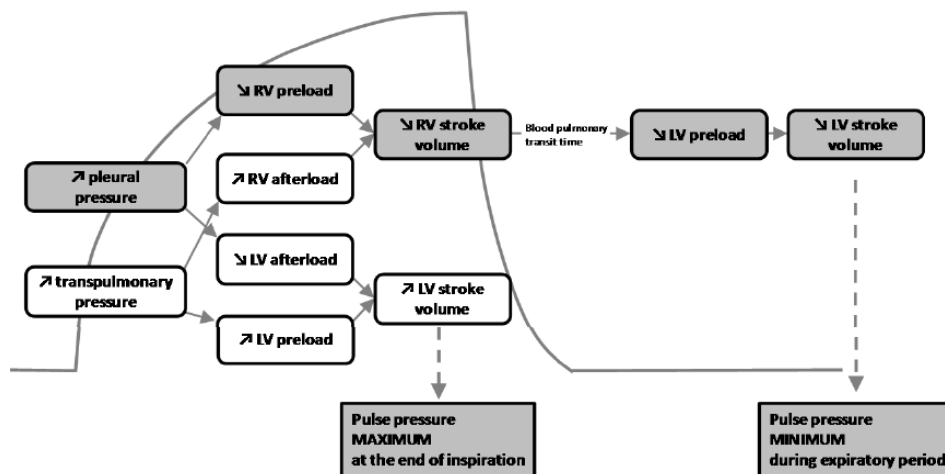


Figure 3: Hearth-lung interactions, hemodynamic effects of mechanical ventilation. (22)

3.3 INDICATORS OF FLUID RESPONSIVENESS

During the past 20 years, a number of tests for predicting volume responsiveness have been developed to allow the clinician to determine the individual patient’s position on his/her Frank-Starling curve, and thus determine whether the patient is likely to be fluid-responsive or not (22) (Table 1). The need for predictors of fluid responsiveness is high to select patients who might benefit from fluid loading, and thereby avoiding ineffective and potentially deleterious fluid administration in situations where inotropics may better be used (1).

Several indicators have been used to test preload responsiveness (Table 1). We can classify them in static and dynamic indicators, latest recommendations are to use dynamic rather than static indicators, when possible, to predict fluid responsiveness (1,12,24,26,30–32). However, in routine clinical practice, the conditions necessary to predict fluid responsiveness with dynamic indicators are not usually met (1,7), a recent prospective French study reported an incidence of 17% of instances where the reliability of PPV and SVV could be used without limitation in ICU, while in the operating room setting, PPV and SVV monitoring can be applied more frequently (33).

To choose the correct test for each clinical situation, it is important to keep in mind that each one has its limitations and different diagnostic thresholds (Table 2). These tests dynamically monitor the change in stroke volume after a maneuver that increases or decreases

STATIC PARAMETERS	DYNAMIC PARAMETERS
Differential arterial pressure	Systolic arterial pressure variation
Mean arterial pressure	Diastolic arterial pressure variation
Central venous pressure	Stroke volume variation
Pulmonary artery occlusion pressure	
Heart rate	
Diuresis	

venous return or preload (22).

Table 1: Static and dynamic parameters for predicting fluid responsiveness (23).

3.3.1 STATIC INDICATORS OF FLUID RESPONSIVENESS

Static indicators as Central Venous Pressure (CVP), pulmonary artery occlusion pressure, the global end-diastolic volume measured with transpulmonary thermodilution, left ventricular end-diastolic dimensions measured by echocardiography and the flow time of aortic flow by esophageal Doppler, are all bad indicators of fluid responsiveness (7). The inability to reflect preload responsiveness is given again by the shape of the Frank-Starling curve which can vary from one patient to another or even can change in a patient from one time to another (7) (Figure 2).

Method	Threshold	Main limitations
Pulse pressure/stroke volume variations [22]	12%	Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/ lung compliance
Inferior vena cava diameter variations [44]	12%	Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Superior vena caval diameter variations [44]	36%*	Requires performing transesophageal Doppler Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Passive leg raising [55]	10%	Requires a direct measurement of cardiac output
End-expiratory occlusion test [75]	5%	Cannot be used in non-intubated patients Cannot be used in patients who interrupt a 15-s respiratory hold
*Mini"-fluid challenge (100 mL) [84]	6%**	Requires a precise technique for measuring cardiac output
*Conventional" fluid challenge (500 mL) [81]	15%	Requires a direct measurement of cardiac output Induces fluid overload if repeated

* Thresholds from 12 to 40% have been reported
 ** 10% is more compatible with echography precision. Citations indicate the most important reference regarding the test

Table 2 Summary of methods predicting preload responsiveness with diagnostic threshold and limitations (7)

CVP has been used for decades to test preload responsiveness and it has been demonstrated as unreliable (7,12,34,35), more than 100 studies have been published demonstrating no relationship between CVP or its change and fluid responsiveness in various clinical settings (34). CVP is a good approximation of right atrial pressure which is a major determinant of RV filling, and because RV stroke volume determines LV filling, CVP is assumed to be an indirect measure of LV preload (7). However, there are other factors that can influence on its measure such as changes in venous tone, intratorathic pressures or LV and RV compliance (22). At any rate CVP is a key determinant of cardiac function, organ perfusion and a good marker of preload, but not preload responsiveness (7). Yet despite this, several studies showed that static markers of preload as CVP are still used in intensive care units and in the operating room (36,37), although many authors and works have recommended not to use CVP

routinely for guiding fluid management in the ICU, operating room, or emergency room (7,22,34).

A static value could correspond to preload responsiveness as well as preload unresponsiveness, depending on the shape of the Frank-Starling curve, and that is a limitation of all static values like CVP named before (1,7).

The measure of **left ventricle end diastolic volume** obtained with echocardiography has been introduced as a clinical variable to assess the preload, nevertheless, it has limitations like the learning curve and the impossibility of continuous monitoring for a long time (2). It has also been demonstrated that it is not a good predictor of fluid responsiveness (38)

The **global end-diastolic volume** (GEDV) measured with transpulmonary thermodilution is the sum of all volumes at the end of diastole in the atria and ventricles, being equivalent to preload. Mathematical analysis of transpulmonary thermodilution curve and the continuous measure of cardiac output, based in pulse contour analysis offers the possibility of measuring GEDV (2). GEDV measured with transpulmonary thermodilution is the only static measure that can reflect preload and fluid responsiveness and, unlike dynamic parameters, its measure is not influenced by spontaneous breathing (2)

3.3.1 DINAMIC INDICATORS OF FLUID RESPONSIVENESS

The first method developed for the dynamic assessment of preload responsiveness was **stroke volume variation (SVV)** (7). SVV is a naturally occurring phenomenon in which the arterial pulse pressure falls in inspiration and rises during expiration due to changes in intra-thoracic pressure, secondary to negative pressure ventilation in spontaneous breathing (23).

Traditionally, SVV is calculated as:
$$SVV = (SV_{max} - SV_{min}) / SV_{mean}$$

over a respiratory cycle or other period of time (23). For measuring SVV, mechanical ventilation can be used as a provocative test where the patient needs to be using positive pressure ventilation (7,23). The rationale is that, during positive pressure ventilation, insufflations decrease preload of the right ventricle, inducing a decrease in preload of the left ventricle that leads to diminution in left stroke volume (SV) (SV_{min}) (23), and during expiration the opposite situation occurs (SV_{max}) (Figure 4). If left ventricular stroke volume changes in response to cyclic positive pressure ventilation, this indicates that both ventricles are preload dependent (7).

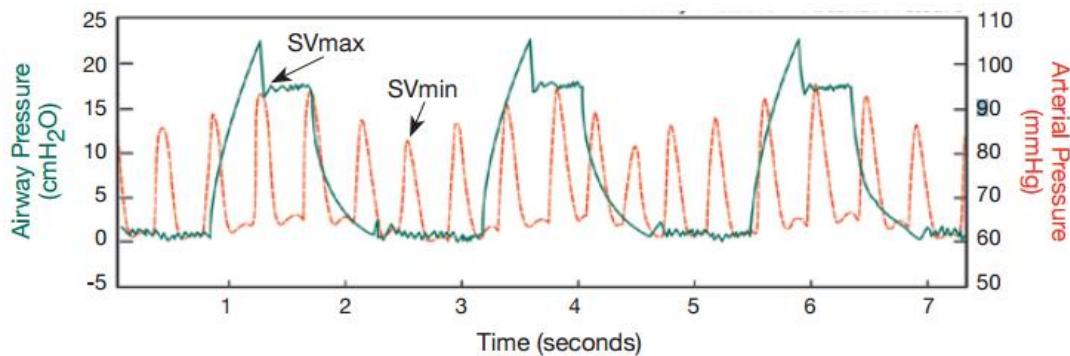


Figure 4: Stroke volume variation in controlled ventilated patients (23)

Pulse pressure variation (PPV) is the comparable measurement to SVV. Arterial pressure rises during inspiration and falls during expiration due to changes in intra-thoracic pressure secondary to positive pressure ventilation (23). In recent years, PPV has accumulated a large amount of evidence (26,39,40). PPV is obtained directly from the peripheral arterial pressure waveform, while SVV can be peripherally derived from subsequent pulse contour analysis of

this arterial pressure waveform, but both peripherally derived parameters are an accurate reflection of central SVV (1). A value of PPV above 12% has shown to be highly predictive of fluid responsiveness (1)

SVV and PPV are not preload indicators, but indicators of relative response to preload (23)

It is important to understand that there are some circumstances depending on the situation of the patients, which can affect the measure of SVV and PPV (2) (Table 2)

Tidal Volume	Needs to be >8ml/kg, large enough to facilitate significant changes in preload (23,41)
Open Thorax	Increases intrathorathic pressure. Dynamic indicators are not useful (2)
Intraabdominal Hypertension	Controversial (see text for more information)
PEEP	Increases intrathorathic pressure. No diagnostic threshold (2,23)
Spontaneous Breathing	SVV was found to be inaccurate in patients with spontaneous breathing activity (23,42)
Arrhythmia	SVV and PPV become highly variable and inaccurate with arrhythmias such as atrial fibrillation (1,23)
Vascular tone	Should be considered as it can lead to inaccurate SVV (23)
Very high respiratory rate (RR)	False negative (7) if RR is >35 (23)
Right heart failure	The increase in right ventricular afterload could be responsible of some false positives in SVV and PPV(7,23)
Heart rate (HR)	Should be < 150 bpm (23)

Table 3. Limitations of SVV and PPV as predictors of fluid responsiveness.

Cyclic changes in intrathorathic pressure and in tidal volume can reflect changes in stroke volume (SV) by reducing venous return, which can be further diminished in an hypovolemic situation (2). Changes in dynamic indicators are more reliable when TV is high (2), many studies assessed that SVV and PPV are good predictors only when TV is at least 8 ml/kg (1,2,7,23). The use of dynamic indicators and its variation cannot be used in patients undergoing thorax surgery because of the changes in intrathorathic pressure (2). The same pathophysiology explains that increases in positive end expiration pressure (PEEP) make difficult the evaluation of dynamic indicators (23), besides, diagnostic threshold for VVS is not defined when PEEP is used.(2) As it has been explained before, SVV and PPV cannot be

measured during spontaneous breathing due to the influence of changes in intrathoracic pressure during its measure (1,2,22,42).

It has been postulated that noradrenalin is a drug that can induce changes directly in capacitance vessels (2) where the major proportion of blood volume resides in (1), altering PPV and SVV (2). It is necessary to take into account that, evaluating dynamic indicators with apparatuses based on pulse pressure waveform in situations when there are changes in vascular tone, makes SVV and PPV values less reliable. However, later versions of these machines have improved their precision in patients with sepsis or alteration in vessel contractility (23).

If intraabdominal hypertension (IH) affects venous return is a controversial issue. Some authors postulate that IH can decrease venous return as a consequence of inferior vena cava compression and collapse (2,43,44). However, other authors, and among them, Monnet et al, postulate that the position in which PLR is done, decreases IH by reducing the weight of the diaphragm and thorax on the abdominal cavity (43). Accurate investigation in this issue is needed to understand the real effect of IH during PLR, thus the question remains unsolved.

3.4 FLUID RESPONSIVENESS IN CLINICAL PRACTICE

The most common and validated way to predict fluid responsiveness in clinical practice is either to use a SVV or a CO monitoring system. Although the ideal situation would be to use SVV, very often, criteria needed for using SVV cannot be applied in our patients because of their comorbidities or their clinical situation.

However, to predict fluid responsiveness using CO monitoring, two methods must be combined, to generate the changes in preload on one hand, and to measure de subsequent changes in stroke volume on the other hand (1).

3.4.1 PASSIVE LEG RAISING TEST

Passive Leg Raising (PLR) test is a diagnostic tool for prediction fluid responsiveness which can be considered as a reversible or *virtual* fluid challenge (43) of around 300mL of blood (45). The maneuver consists in moving the patient to a position in which the trunk is horizontal and the lower limbs are lifted at 45°, mobilizing some venous blood from the lower limbs and the abdomen toward de cardiac cavities (7,43). PLR promotes venous return and increases right and left cardiac preload to an extent that is sufficient to challenge preload responsiveness of both ventricles (46) with a maximum increase within the first 60 or 90 seconds (1,23). PLR test is now accepted as a test for predicting fluid responsiveness in clinical practice, having recently been recommended by a consensus conference of the European Society of Intensive Care Medicine (12) and has also been implemented in the bundles of the Surviving Sepsis Campaign (47).

The importance of the correct positioning of the patient when performing the PLR test has been studied, and it has been widely demonstrated that starting the maneuver from semi-recumbent position augments the effects of the test on cardiac preload. (7,22,43,45,48).

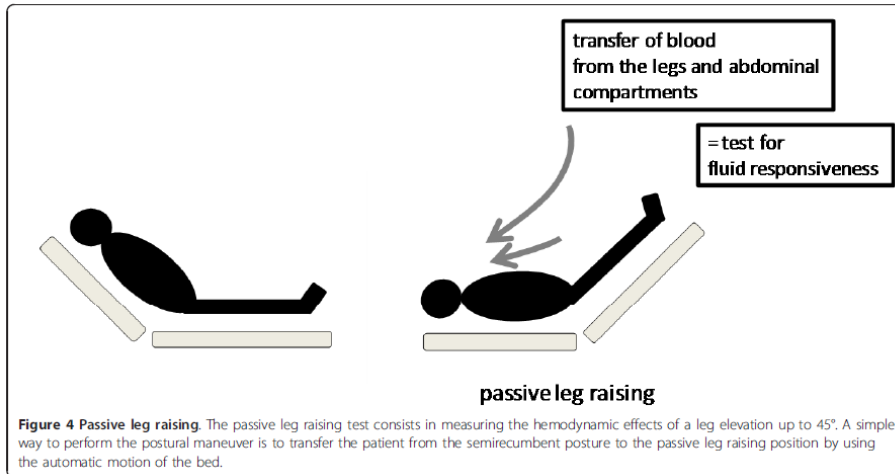


Figure 5: Passive leg raising test maneuver (22).

One of the advantages of PLR test is that it can be used in instances in which the fluid responsiveness based on SVV is not reliable (spontaneous breathing, cardiac arrhythmias, low lung compliance and low tidal volume) (49)

Since PLR is insufficient to induce a significant increase in arterial pressure (43,50), effects of the PLR must be assessed by the direct measurement of CO (7,43). Other of the main advantages of PLR is that, a meta-analysis in 2010 demonstrated that PLR-induced changes in cardiac output (CO) predicted fluid responsiveness regardless of the technique of CO measurement (50), thus PLR-induced changes in cardiac output (CO) can be measured with methods that are able to track changes in CO or stroke volume on a real-time basis. Echocardiography, pulse contour analysis, esophageal Doppler, bioreactance and photoplethysmography have demonstrated similar results (7,43).

An important point to keep in mind about PLR test and other methods for predicting fluid responsiveness is that a positive PLR test should not systematically lead to administering fluid, this decision should be made taking into account the clinical situation of the patient, since fluid responsiveness is not associated with improved outcome. (43)

3.4.2 VIGILEO/FLOTRAC SYSTEM

Vigileo/FloTrac system from Edwards Lifesciences, is a minimally invasive hemodynamic monitoring based on pulse pressure waveform analysis, that enables the clinician to monitor on real time CO, SV, SVV, cardiac index, stroke variation index and peripheral vascular resistance (PVR) (Annex 2) using a complex algorithm.(23,51) This algorithm (Annex 2) is based on the principle that pulse pressure is proportional to SV and is inversely related to aortic distensibility (23).

The FloTrac system is a specific pressure transducer attached to any commercially available arterial catheter and connected to a specific monitor (Vigileo). (52)

Channeling radial artery, FloTrac algorithm calculates CO correlating the variance between systolic and diastolic pressure and compensating for changes in vascular physiology affecting the pressure waveform every 20 seconds (23). Vessel compliance is estimated from nomograms based on age, gender, height, and weight; and peripheral resistance is determined from arterial waveform characteristics (52).

However, Vigileo/FloTrac system shouldn't be used in all situations, although it has lately improved its efficiency in many clinical situations, its use is still being disputed in extreme vasodilatation, hyperdynamic circulation, hepatic cirrhosis, intraaortic counter-pulsation balloons and aortic regurgitation (23).

Vigileo/FloTrac system is a good tool used in patients under major surgery or hemodynamically unstable to help optimizing the therapy the patient is receiving (23,51), it's a good tool to understand better and more accurately the clinical situation of the patient. It is also a valid, easy to use option for predicting fluid responsiveness as it's shown in Figure 6.

An increase in pulse contour analysis calculated CO by more than 10% in response to PLR has been shown to accurately predict volume responsiveness in mechanically ventilated patients with spontaneous breathing activity (43,53,54).

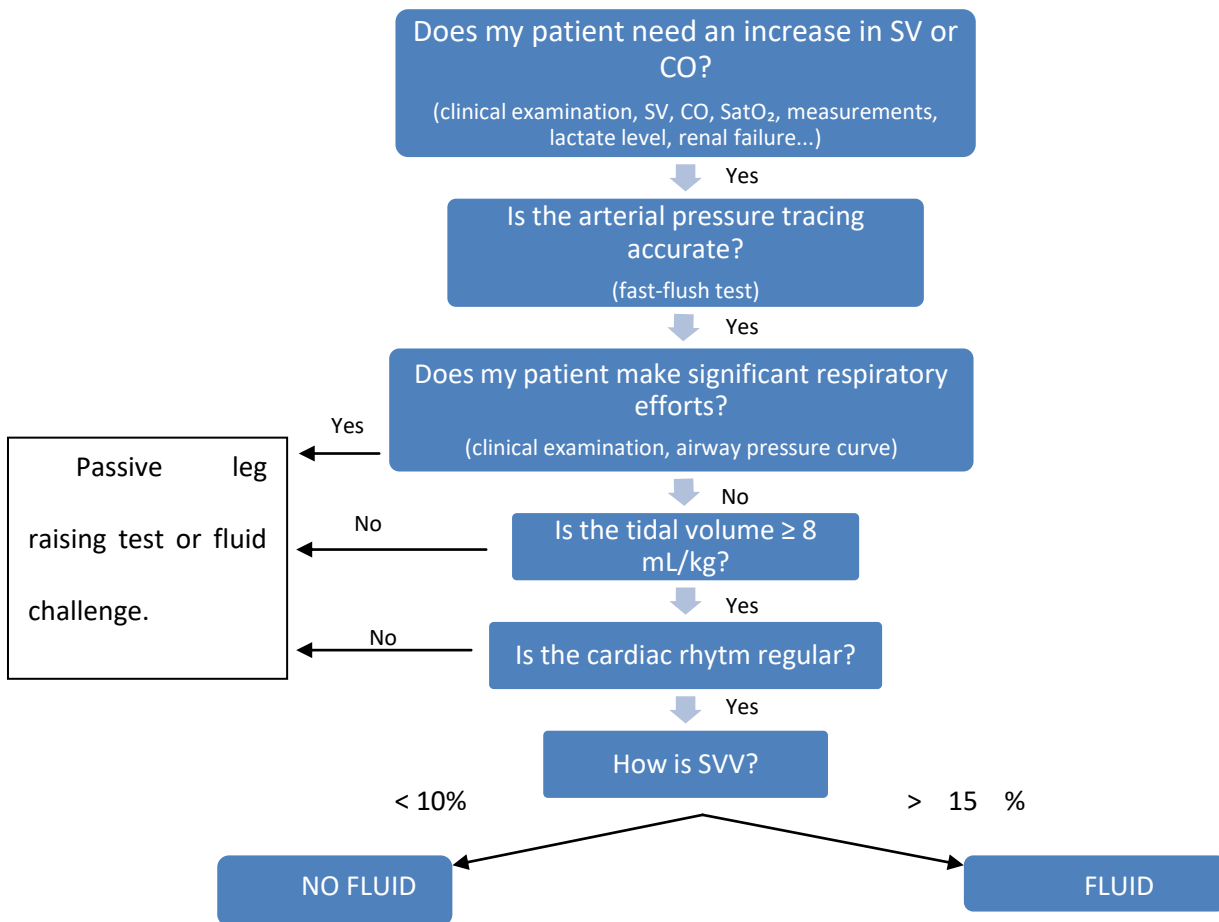


Figure 6: How to assess Stroke volume variation in clinical practice. Adapted from (32)

3.4.3 OTHER TECHNIQUES

When assessing fluid responsiveness, a fluid challenge of 500 mL can be administered, but fluid challenge has two major drawbacks, firstly it requires a direct measurement of cardiac output and cannot be based solely on arterial pressure changes; secondly, the fluid challenge is not a test but a treatment itself, and patients who need more than one fluid challenge, will receive unnecessary fluid loading (1,7). To avoid these disadvantages, a “mini-fluid” challenge with 100 mL colloid has been described, and effects of both, the fluid challenge with 500 mL and mini-fluid challenge with 100 mL, can be assessed with Vigileo/FloTrac system to obtain parameters as CO, SV, cardiac index, stroke volume index, SVV or PVR (23).

After invasive arterial pulse pressure, many other surrogates of stroke volume have been investigated to assess SVV during mechanical ventilation and research has focused on less invasive and non invasive techniques (7). The ventilation-induced variations in arterial pulse pressure estimated by photoplethysmography (55), SV measured by pulse contour analysis, the velocity time integral of the flow in the left ventricular outflow track at echocardiography, the aortic blood flow by esophageal Doppler (56), GEDV measured with transpulmonary thermodilution (2) and the amplitude of the plethysmographic signal (57,58) have been established as preload responsiveness indicators (26,39).

Although it is not possible to monitor them continuously, echocardiographic assessment of inferior and superior vena cava diameter and collapsibility, respectively, have shown to accurately predict fluid responsiveness (7,59). However it requires transesophageal echocardiography (22), with its limitations and lack of availability and it has been less well studied without an established diagnostic threshold and less specificity and sensitivity (7,60,61).

Various other methods have been developed, such as the end-expiratory occlusion test, the respiratory systolic variation test (RSVT) and PEEP-induced change in hemodynamic parameters, to predict fluid responsiveness while avoiding many of the caveats existing for SVV and PPV, and they appear to be as accurate as PPV and SVV (7,62,63). The end-expiratory occlusion (EEO) test consists on interrupting mechanical ventilation for at least 15 seconds (53), removing the positive pressure from the machine and increasing cardiac preload transiently, if cardiac output increases in response to this EEO, it indicates preload responsiveness of both ventricles (7).

4. JUSTIFICATION

Traditionally used parameters to understand patient's hemodynamical situation such as arterial blood pressure, mean arterial pressure (MAP), HR or CVP, have been demonstrated as unable to predict fluid responsiveness (7,22), although they are indispensable for the management of a critically ill patient in ICU, in the operating room or in the emergency room.

In recent years, new parameters have been developed to better understand fluid responsiveness, and among them SVV and CO monitoring systems have gained importance thanks to new minimally invasive systems available for their measurement. Vigileo/FloTrac pulse contour analysis system is one of these minimally invasive techniques which is being used worldwide in patients undergoing major surgery, allowing the clinician to have more information of the patient's cardiocirculatory state (23). As medicine evolves to individualization of cancer treatments, many other disciplines are doing the same, as for example, the resuscitation of a critically ill patient.

PLR maneuver, which has been traditionally used as a treatment for dizziness, it's now a useful test that can be performed in almost all clinical situations. Since PLR is defined by some authors as an autotransfusion(7,22,43), we have developed the hypothesis that staggering PLR could be useful for establishing degrees of fluid responsiveness.

Staggered passive leg raising (SPLR) test consists on an adaptation of PLR test, which adds one step to this test by performing one-leg PLR before the traditional two-leg PLR. If our hypothesis is confirmed, this study could be the first step being able to give the patients a more individualized fluid therapy, based on each patient specific needs. The modification of the PLR test into stages (SPLR test) could differentiate and classify patients who are fluid responders into two groups: *partial* fluid responders (the ones that only are responders to one-leg PLR), or *total* fluid responders (the ones who are responders to both, one-leg PLR and two-leg PLR).

5. HYPOTHESIS

Changes in SVV and CO assessed by the Vigileo/Flo-track during the Staggered Passive Leg Raising test are a useful tool to evaluate several degrees of fluid responsiveness in mechanically ventilated patients.

6. OBJECTIVES

6.1 MAIN OBJECTIVE

To evaluate if SPLR test can trigger significant changes on CO, SVV and MAP assessed by Vigileo/Flotrac device in mechanically ventilated patients attending Hospital Universitari Josep Trueta of Girona for a major surgical process.

6.2 SECONDARY OBJECTIVES

- To define the proportion of patients who have SVV $\geq 12\%$ during one-leg PLR and also SVV $\geq 14\%$ during two-leg PLR (*partial* fluid responders).
- To define the proportion of patients who have SVV $\geq 12\%$ during one-leg PLR and also SVV $\leq 14\%$ during two-leg PLR (*total* fluid responders).

7. METHODS

7.1 STUDY DESIGN

The study is a Hospital based, observational, cross-sectional, study with a consecutive method of sampling of patients attending the operating room of Hospital Universitari Josep Trueta in Girona for a major surgery procedure that meet the inclusion criteria.

Data will be collected before starting surgery.

7.2 PARTICIPANTS

The participants in the study will be patients between 18 and 70 years attending the operating room in Hospital Universitari Josep Trueta for a major surgery who due to the aggressiveness of the surgery, will need monitoring with Vigileo/FloTrack device, CVP and mechanical ventilation during the surgery, and who meet the inclusion criteria.

7.2.1 INCLUSION CRITERIA

All five inclusion criteria must be present:

- Mechanical ventilated patients
- Sinusal rhythm
- Need of Vigileo/Flo-Track device for monitoring during the surgery
- Between 18 and 70 years
- SVV > 10%

7.2.2 EXCLUSION CRITERIA

- Valvular heart disease
- Intracardiac shunts
- Preoperative arrhythmia

- Regional myocardial asynchrony
- Peripheral vascular disease
- Ejection fraction less than 30%
- Pacemaker carriers
- Need of cardiac support (pacemaker or intra-aortic balloon pump carriers).
- Amputation of any of the lower members
- Osteoarthritis
- Need of vasoplegic drugs
- Septic shock
- Diabetic neuropathy

7.3 SAMPLE

7.3.1 Sample size

Calculation of the sample size has been done using GRANMO application, taking in account that SVV is the most important variable for our study, and based on data published by other studies (64,65).

Assuming a standard deviation of 4 for this variable, a loss rate of 0%, and accepting an alpha risk of 0.05 and a beta risk under 0.2 in a bilateral contrast, 32 subjects will be needed to detect a difference equal or greater than 2 standard deviations in mean SVV.

In Hospital Universitari Josep Trueta, at least 5 patients per week go through a major surgical procedure; therefore the time needed for collecting all the data necessary for our study will be approximately of 7 weeks.

7.3.2 Sample selection

Subjects included in the study will be patients attending the operating room in Hospital Universitari Josep Trueta of Girona for a major procedure that will need general anaesthesia, mechanical ventilation and Vigileo/FloTrac system monitoring, meeting the inclusion and exclusion criteria.

Patients attending the study will be selected at the operating room, after the evaluation in preanesthetic consultation where potential candidates will be evaluated.

8. VARIABLES AND MEASUREMENTS

All the data will be collected into the case-report form attached in Annex 1 in four moments (baseline status, during SPLR and after a fluid bolus) and registered with Edwards-Vigileo/FloTrac system which has shown its validity and reproducibility in different clinical situations (66–68). As Vigileo/FloTrac system gives constant information of the parameters, we will collect the data of our variables once in each of the four steps of data collection.

MAIN VARIABLES

Stroke volume variation It is a quantitative discrete variable calculated as

$$SVV = \frac{SV_{max} - SV_{min}}{SV_{mean}} \text{ over a respiratory cycle (23).}$$

Cardiac output is a quantitative continuous variable, calculated with FloTrac algorithm as $COAP = FP \times ds(PA) \times \chi$ (23) (see Annex 2). Cardiac output depends on age, stress, metabolical state and corporal surface among others (28).

Mean Arterial Pressure is a quantitative continuous variable that can be calculated as

$$MAP = DP + \frac{1}{3} (SP - DP). (28)$$

For our secondary objective, if statistical analysis shows differences between mean SVV, CO and MAP in several measurements during SPLR test; we will classify the patients into two categories using a new dichotomous variable defined by us as fluid response to SPLR:

- **Partial fluid responders**, defined as patients who show a $SVV \geq 12\%$ during one-leg PLR and a $SVV \geq 14\%$ during two-leg PLR.
- **Total fluid responders**, defined as patients who show a $SVV \geq 12\%$ during one-leg PLR and a $SVV \leq 14\%$ during two-leg PLR.

This classification will allow us to analyze if describing several degrees of fluid responsiveness is possible.

COVARIATES

Age (measured in years) and **Gender** (female or male)

9. DATA COLLECTION AND STUDY CIRCUIT

During 7 weeks, medical personal of the department of Anesthesiology and Reanimation of Hospital Universitari of Girona who participate in the study, will collect the data from every patient that fulfils the criteria of our study, using the case-report form (Annex 1). Data will be collected in the operating room, before starting the surgery.

PREPARATION

Before starting anesthetic induction and during preoperative period, patients will be monitored with pulseoxymeter for SatO₂, sphygmomanometer to control systolic pressure, MAP and diastolic pressure, five-lead electrocardiography, and oxygen with facial mask. All measures will be in accordance with institutional standards.

As we explained before, drugs used in anesthetic induction can have different hemodynamic effects, hence the importance of a standardized anesthetic induction and maintenance for our study. For the anesthetic induction we will use:

- Midazolam: 1 to 5 mg intravenous, in relation with weight and age. This is the dose used in clinical practice to decrease the patient's preoperative anxiety.
- Fentanyl: 2 mcgr/kg
- Propofol: 1'5 to 2'5 mg/kg in relation with basal status and age of the patient.
- Rocuronium: 0'5 mg/kg.

After anesthetic induction we will proceed to orotracheal intubation (OTI) and anesthetic maintenance will be done with Sevoflurane maintaining a minimum alveolar concentration between 0,5% and 1%. Mechanical ventilation will be maintained with a General Electric Ventilator using a volume-controlled mode: tidal volume \geq 8 ml/kg, and RR of 12 breaths per minute.

With the patient anesthetized, we will carry out the placement of the catheter in the radial artery to start minimally invasive monitoring with Vigileo/FloTrac device, providing invasive blood pressure measurement, CO, SVV, PVR, and cardiac index. Monitoring of CVP will also be

needed for intraoperative hemodinamical monitoring. Later, a heavy gauge cannula will be channeled, to use just in case it is needed during the surgery. This process should last between 15 and 20 minutes, which is time enough for the patient to stabilize after the anesthetic induction and OTI.

DATA COLLECTION

With the patient stabilized and anesthetized with Sevofluorane ensuring a minimum alveolar concentration between 0.5 % and 1% and a SVV >10 % we will proceed to data collection.

Baseline determination will be done first with the patient in the semi recumbent position: head elevated 45°. As the patient will be lying on supine position during the preparation process, after the change to the semi recumbent position, we will wait 2 minutes until his/her body stabilizes in the new position.

The second determination will be done while elevating one leg (one leg-PLR test). It is important to understand that PLR test always starts from the semi recumbent position (23,45) and legs have to be elevated 45° simultaneously with the descent of the trunk to the supine position. To avoid confounding factors we will elevate the right leg placing a wedge pillow usually used in the operating room to ease intubation of patients with difficult airway. We will collect the data 120 seconds after positional change, when the maximum effect takes place.

Once data of one leg-PLR test are collected, the patient will return to semi recumbent position during 5 minutes, time enough for its body to adapt hemodinamically to the new position. Again, two leg-PLR test will be done starting from the semi recumbent position and elevating legs to 45° simultaneously with the descent of the trunk to the supine position. Data will be collected 120 seconds after positional change, and returning to supine position after it.

Finally, 4 mL/kg of an electrolytic solution will be perfused in 5 minutes (3). This input of liquid is not aggressive after an anesthetic induction in a patient that is in *famis diet* for more than 6 hours. Data will be collected 2 minutes after the infusion.

10. STATISTICAL ANALYSIS

All the statistical variables analysis will be performed using IBM Statistical Package for Social Science (SPSS) version 23.0. Statistical significance will be considered at a p value < 0,5 and confidence intervals will be calculated at 95%.

- **DESCRIPTIVE ANALYSIS**

Results of data collected will be presented as percentages and proportions for categorical variables. For quantitative variables, results of data collected will be presented as mean \pm SD and interquartile range (25-75) depending on whether they have a normal distribution or not.

- **BIVARIATE ANALYSIS**

To study the relationship between mean SSV, CO and MAP repeated measures during SPLR test and after a bolus of fluid, we will use ANOVA analysis for repeated measures.

If the ANOVA analysis for repeated measures shows statistic differences we will assess our secondary objectives by analyzing and describing the proportion of patients defined as *partial* fluid responders or *total* fluid responders.

- **MULTIVARIANT ANALYSIS**

A lineal multiple regression analysis will be conducted in order to adjust the relationship between changes in mean SSV, CO and MAP in the different groups with potential confounders (gender and age) and to give more external validity to our study.

11. WORK PLAN AND CHRONOGRAM

All the study process is expected to last 11 months. Activities carried out during this time will be organized in the following 4 phases.

PHASE 1: PREPARATION AND COORDINATION

This first part of the study lasts two months and consists on the elaboration of the current protocol from November 2016 to January 2017.

In order to specify the tasks every member of the team will be in charge, investigators, collaborators and statisticians will meet. The methods of data collection will be discussed and set up, and the chronogram will be corrected with the collaboration of the members of the research team. Also during this meeting we will instruct all the researchers participating in the data collection process to ensure it is correct. Once the protocol is approved by all the team participating and ready, we will present it to the Ethical Committee of Hospital Univeristari Josep Trueta for its evaluation and approval.

In order to control de data collected, asses the progress of the study, identify deficiencies and correct methodological flaws, the researchers will meet once.

PHASE 2: DATA COLLECTION

This part of the study lasts 7 weeks and consists on the selection of the patients with the inclusion/exclusion criteria described before, and data collection.

Data collection will be carried out using a pre-established form attached in Annex 1 and the entire process should last 30 or 45 minutes to avoid hindering the work in the operating room.

PHASE 3: STATISTICAL ANALYSIS PROCESS

After processing the database, all data will be analyzed using the appropriate statistical tests by an external statistician. This part of the study should last 1 month.

Conclusions and results will be extracted and evaluated by all the research team.

PHASE 4: PUBLICATION AND DISSEMINATION

During the last two months, the researchers will write and edit a scientific paper to publish.

CHRONOGRAM

STAGES	2016			2017							
	N	D	J	F	M	A	M	J	J	A	S
Phase 1: Preparation and coordination (November 2016 - March 2017)											
Protocol elaboration and evaluation											
Research team coordination meeting											
Ethical approval											
Phase 2: Data collection (April 2017 – May 2017)											
Data collection process											
Phase 3: Statistical analysis (June 2017 – July 2017)											
Statistical analysis											
Evaluation of results											
Phase 4: Publication and dissemination (July 2017 – September 2017)											
Final article elaboration											
Results publication											

12. BUDGET AND FEASIBILITY

EXPENSES	COSTS
PERSONAL EXPENSES	
Investigator team	0 €
EXECUTIVE EXPENSES: Material and services	
Statistical specialist (25 hours; 35 €/hour)	700 €
Office consumables and others	100€
Electrolytic solution (32 units, 3.04€/unit)	97,28€
PUBLICATION AND DISSEMINATION	
Publication costs (Inscriptions, transport and accommodation to national and international appointments)	2000€
	TOTAL: 2.897,28€

We consider that activities needed for the study don't compromise normal clinical assistance. All the patients selected for the study will be patients that would need a Vigileo/FloTrac system for the hemodynamic monitoring of the surgery, meaning that no higher cost has to be assumed for the realization of the study.

Given that the means in terms of personal and material are already available, once the study is accepted by the ethics committee and the budget is approved, it can be carried out complying with all aspects involved in this protocol.

13. STRENGTHS AND LIMITATIONS

Several limitations of this study should be acknowledged.

Our study is designed as a descriptive cross-sectional study. With this design, we cannot establish causal inferences; therefore we will only be able to talk about an association between our variables.

Selection bias could be present for two reasons, firstly, because a non-probabilistic consecutive sampling method has been chosen for the study. And secondly because the study has been designed to collect the data on the moment after the anesthetic induction, when patients are not in a ideal stable state due to the perioperative processes (vasodilator effects of anesthetic drugs, intubation, channeling radial artery and a central vein). The ideal situation would have been to do it in reanimation room, but few patients in our hospital meet the criteria we needed there, and the inclusion period of our study would have been too long.

It is possible to have covariables producing confusion which we have not considered before in the multivariate analysis, for example the previous volemic status of the patient which is very difficult to approach.

Since several people will be collecting the data, we are aware that there could be a bias in the data collection process, for minimizing this risk, we will have a meeting with all researchers participating in the study to explain the exact process and to ensure everybody fills the case-report form in the same way.

This study also has some strengths that are worth remarking. The loss of participants will be zero, as they will be selected in the moment they enter the operating room and all the data collection process for the study doesn't change the patient's management. Thus the work has high feasibility, as it won't involve many expenses. Besides, SPLR test hasn't been described in any other study before.

14. IMPACT OF THE STUDY

Fluid responsiveness is a relatively new concept developed specially in critical care context that is getting introduced in clinical practice. Many techniques for predicting fluid responsiveness have been discovered in the last 15 years and, like in every medical attention, most aggressive techniques are being substituted by minimally invasive techniques, as for example PLR test.

Fluid responder patients are always treated with the same dose of fluids, and it has been demonstrated that an accurate fluid therapy adapted to the patient real needs was related to less complications. Thus, we asked ourselves if a modified PLR test could guide to several degrees of fluid responsiveness, and for answering that question we have developed this protocol describing SPLR test.

If our hypothesis is confirmed, this work could be the first step for predicting several degrees of fluid responsiveness and to personalize fluid therapy, to deepen the idea that fluid is a treatment itself and should'nt be overdosed or underdosed, showing the importance of adjusting the dose to the patient real needs.

Obviously further studies will be necessary to confirm our hypothesis and to show evidence that SPLR test is a good predictor of several degrees of fluid responsiveness.

15. ETHICAL CONSIDERATIONS

As regulated by the law 14/2007 of the 3rd of July about biomedical investigation, this study will have to be approved by the Clinical Research Ethics Committee (CEIC, Comitè d'Ètica d'Investigació Clínica) of the Hospital Universitari Josep Trueta in Girona.

This study is conducted according to the requirements expressed in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects signed by the World Health Association the October 2013, and to ministerial order SAS/3470/2009 defined in the current legislation in Spain related with the conduct of observational studies.

All participants will be informed about the interventions and the details of this intervention study. They will participate voluntarily in the study and will be given an Information Sheet (Annex 4) and Informed Consent Sheet (Annex 3) for the inclusion in the study. It is imperative that patients read and understand the information sheet and sign the informed consent forms too. Thereby, the principle of autonomy will be respected. In case of incapability, we will seek informed consent from their legally authorized representative.

In addition, the processing of personal data required in this study, its communication, the personal data cession of all the patients and the confidentiality is in compliance with Spanish Law 15/1999 of December 13 on the Protection of Personal Data (LOPD) and with the Royal Decree 1720/2007 of December 21 of the Development of the Organic Law on Data Protection. Patient data, including clinical history information, names and surnames, remain anonymous when introducing and processing this information into a database, which will also be handled according to the mentioned Law and exclusively used for the development of the study. Moreover, in order to guarantee the confidentiality of the survey data, the access will be only restricted to the research team, the Ethical and Clinical Investigation Committee, the pertinent health authorities and those responsible for data analysis. The content of the database and the documents generated during the study will be protected from not permitted uses of alien persons, and therefore, considered strictly confidential and will not be disclosed to third

parties except those already specified. For that reason, membership of the research team, the hospital and the collaborators participating in the study, must sign a statement attesting to having read and approved the final protocol, and agree with the national and international ethical aspects with the investigation (Annex 5). All investigators will have to declare no conflict of interest.

16. BIBLIOGRAPHY

1. Cherpanath TG V, Geerts BF, Lagrand WK, Schultz MJ, Groeneveld ABJ. Basic concepts of fluid responsiveness. *Neth Heart J* [Internet]. 2013 Dec [cited 2017 Jan 11];21(12):530–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24170232>
2. Casanova MPR, Garcia Peña JM, Lomillos Rafols V, De Luís Cabezon N, Aguilera Celorrio L. Fluidoterapia perioperatoria. *Rev Esp Anesthesiol Reanim*. 2010;57:575–85.
3. NICE. Intravenous fluid therapy in adults in hospital. National Institute for Health and Care Excellence; 2013.
4. Gould TH, Grace K, Thorne G, Thomas M. Effect of thoracic epidural anaesthesia on colonic blood flow. *Br J Anaesth* [Internet]. 2002 Sep [cited 2016 Dec 11];89(3):446–51. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12402724>
5. Biais M, Bernard O, Ha JC, Degryse C, Sztark F. Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. *Br J Anaesth* [Internet]. 2010 Apr 1 [cited 2016 Dec 11];104(4):407–13. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20190260>
6. Basora M, Colomina MJ, Moral V, Asuero de Lis MS, Boix E, Jover JL. Guía de práctica clínica para la elección del fluido de restauración volémica perioperatoria en los pacientes adultos intervenidos de cirugía no cardiaca. *Rev Esp Anesthesiol Reanim*. 2016;63(1):29–47.
7. Monnet X, Marik PE, Teboul J-L, Rivers E, Nguyen B, Havstad S, et al. Prediction of fluid responsiveness: an update. *Ann Intensive Care* [Internet]. 2016 Dec 17 [cited 2016 Nov 28];6(1):111. Available from: <http://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-016-0216-7>
8. Lobo DN. How perioperative fluid balance influences postoperative outcomes. *Best Pract Res Clin Anaesthesiol* [Internet]. 2006 [cited 2016 Nov 29];20(3):439–55. Available from: <http://www.sciencedirect.com>
9. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet* [Internet]. 2002 May 25 [cited 2016 Dec 11];359(9320):1812–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12044376>
10. Benes J, Kirov M, Kuzkov V, Lainscak M, Molnar Z, Voga G, et al. Fluid Therapy: Double-Edged Sword during Critical Care? *Biomed Res Int* [Internet]. 2015 [cited 2016 Dec 11];2015:1–14. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26798642>
11. Lobo DN. Fluid, electrolytes and nutrition: physiological and clinical aspects. *Proc Nutr Soc*. 2004;63:453–66.
12. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofner C, et al. Consensus on circulatory shock and hemodynamic monitoring . Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40:1795–815.
13. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* [Internet]. 2011 Feb [cited 2016 Dec 11];39(2):259–65. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20975548>
14. Vincent J-L, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* [Internet]. 2006 Feb [cited 2016 Dec 11];34(2):344–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16424713>
15. Micek ST, McEvoy C, McKenzie M, Hampton N, Doherty JA, Kollef MH. Fluid balance and cardiac function in septic shock as predictors of hospital mortality. *Crit Care* [Internet]. 2013 Oct 20 [cited 2016 Dec 11];17(5):R246. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24138869>
16. Murphy C V., Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. *Chest* [Internet]. 2009 Jul [cited 2016 Dec 11];136(1):102–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19318675>
17. Rosenberg AL, Dechert RE, Park PK, Bartlett RH, NIH NHLBI ARDS Network. Review of A Large Clinical Series: Association of Cumulative Fluid Balance on Outcome in Acute Lung Injury: A Retrospective Review of the ARDSnet Tidal Volume Study Cohort. *J Intensive Care Med* [Internet]. 2008 Nov 25 [cited 2016 Dec 11];24(1):35–46. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19103612>
18. Jozwiak M, Teboul J-L, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. *Ann Intensive Care* [Internet]. 2015 Dec [cited 2016 Dec 11];5(1):38. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26546321>
19. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain MLNG, De Keulenaer B, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* [Internet]. 2013 Jul 15 [cited 2016 Dec 11];39(7):1190–206. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23673399>

20. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* [Internet]. 2009 Aug [cited 2016 Dec 11];76(4):422–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19436332>
21. Payen D, de Pont A-CJM, Sakr Y, Spies C, Reinhart K, Vincent J-L, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* [Internet]. 2008 [cited 2016 Dec 11];12(3):R74. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18533029>
22. Marik PE, Monnet X, Teboul J-L. Hemodynamic parameters to guide fluid therapy. *Ann Intensive Care* [Internet]. 2011 Mar 21 [cited 2016 Dec 12];1(1):1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21906322>
23. McGee WT, Headley JM, Frazier JA, Lichtenthal PR. *Guia rápida de cuidados cardiorrespiratorios*. 3rd ed. Edwards Lifesciences Corporation; 2014. 234 p.
24. Michard F, Teboul J-L. Predicting Fluid Responsiveness in ICU Patients: A Critical Analysis of the Evidence. *Chest*. 2002;121(6):2000–8.
25. Monnet X, Teboul J-L. Volume responsiveness. *Curr Opin Crit Care* [Internet]. 2007 Oct [cited 2016 Dec 12];13(5):549–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17762234>
26. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Crit Care Med* [Internet]. 2009 Sep [cited 2016 Dec 12];37(9):2642–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19602972>
27. Mohrman DE, Heller LJ. *Cardiovascular physiology*. 6th ed. Minnesota: Lange; 2006.
28. Guyton AC, Hall JE. Gasto cardíaco, retorno venoso y su regulación. In: *Tratado de fisiología médica*. 12th ed. Barcelona: Elsevier; 2011. p. 229–40.
29. Maas JJ, Pinsky MR, Geerts BF, de Wilde RB, Jansen JR. Estimation of mean systemic filling pressure in postoperative cardiac surgery patients with three methods. *Intensive Care Med* [Internet]. 2012 Sep 15 [cited 2017 Jan 23];38(9):1452–60. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22584797>
30. Marx G, Cope T, McCrossan L, Swaraj S, Cowan C, Mostafa SM, et al. Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. *Eur J Anaesthesiol* [Internet]. 2004 Feb [cited 2017 Jan 16];21(2):132–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14977345>
31. Reuter DA, Kirchner A, Felbinger TW, Weis FC, Kilger E, Lamm P, et al. Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. *Crit Care Med* [Internet]. 2003 May [cited 2017 Jan 16];31(5):1399–404. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12771609>
32. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* [Internet]. 2005 Aug [cited 2017 Jan 16];103(2):419–28-5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16052125>
33. Preau S, Dewavrin F, Demaeght V, Chiche A, Voisin B, Minacori F, et al. The use of static and dynamic haemodynamic parameters before volume expansion: A prospective observational study in six French intensive care units. *Anaesth Crit Care Pain Med* [Internet]. 2016 Apr [cited 2017 Jan 16];35(2):93–102. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26603329>
34. Marik PE, Baram M, Vahid B. Does Central Venous Pressure Predict Fluid Responsiveness?*: A Systematic Review of the Literature and the Tale of Seven Mares. *Chest* [Internet]. 2008 Jul [cited 2017 Jan 10];134(1):172–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18628220>
35. Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care* [Internet]. 2010 Aug [cited 2017 Jan 15];16(4):289–96. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20543685>
36. Cecconi M, Hofer C, Teboul J-L, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. *Intensive Care Med* [Internet]. 2015 Sep [cited 2016 Dec 15];41(9):1529–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26162676>
37. Cannesson M, Pestel G, Ricks C, Hoefft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. *Crit Care* [Internet]. 2011 Aug 15 [cited 2016 Dec 15];15(4):R197. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21843353>
38. Renner J, Gruenewald M, Brand P, Steinfath M, Scholz J, Lutter G, et al. Global End-Diastolic Volume as a Variable of Fluid Responsiveness During Acute Changing Loading Conditions. *J Cardiothorac Vasc Anesth* [Internet]. 2007 Oct [cited 2017 Jan 15];21(5):650–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17905268>
39. Yang X, Du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care* [Internet]. 2014 Nov 27 [cited 2017 Jan 16];18(6):650. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25427970>
40. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? *JAMA* [Internet]. 2016 Sep 27 [cited 2017 Jan 16];316(12):1298. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27673307>
41. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent J-L. Pulse pressure variations to predict fluid

- responsiveness: influence of tidal volume. *Intensive Care Med* [Internet]. 2005 Apr 8 [cited 2017 Jan 15];31(4):517–23. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15754196>
42. Perner A, Faber T. Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. *Acta Anaesthesiol Scand* [Internet]. 2006 Oct [cited 2016 Nov 29];50(9):1068–73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16939480>
 43. Monnet X, Marik P, Teboul J-L. Passive leg raising for predicting fluid responsiveness : a systematic review and meta-analysis. *Intensive Care Med*. 2016;42(12):1935–47.
 44. Malbrain MLNG, Reuter DA. Assessing fluid responsiveness with the passive leg raising maneuver in patients with increased intra-abdominal pressure: Be aware that not all blood returns! *Crit Care Med* [Internet]. 2010 Sep [cited 2017 Jan 22];38(9):1912–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20724891>
 45. Jabot J, Teboul J-L, Richard C, Monnet X. Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* [Internet]. 2009 Jan 16 [cited 2017 Jan 19];35(1):85–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18795254>
 46. Boulain T, Achard J-M, Teboul J-L, Richard C, Perrotin D, Ginies G. Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. *Chest* [Internet]. 2002 Apr [cited 2017 Jan 22];121(4):1245–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11948060>
 47. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012. *Intensive Care Med* [Internet]. 2013 Feb [cited 2016 Nov 30];39(2):165–228. Available from: <http://link.springer.com/10.1007/s00134-012-2769-8>
 48. Monnet X, Teboul J-L. Passive leg raising: five rules, not a drop of fluid! *Crit Care* [Internet]. 2015;19(1):18. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4293822&tool=pmcentrez&rendertype=abstract%5Cnhttp://ccforum.com/content/19/1/18>
 49. Monnet X, Teboul J-L. Assessment of volume responsiveness during mechanical ventilation: recent advances. *Crit Care* [Internet]. 2013 Mar 19 [cited 2017 Jan 22];17(2):217. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23510457>
 50. Cavallaro F, Sandroni C, Marano C, La Torre G, Mannocci A, De Waure C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med* [Internet]. 2010 Sep 26 [cited 2017 Jan 22];36(9):1475–83. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20502865>
 51. Soriano Pérez ÁM, Galindo de Blas B, González Fernández R, Galán Ocaña A. Vigileo: Monitorización mínimamente invasiva del gasto cardiaco y oximetría venosa. *Rev médica Jaén*. 2014;4:13–6.
 52. Cannesson M, Musard H, Desebbe O, Boucau C, Simon R, Hénaine R, et al. The Ability of Stroke Volume Variations Obtained with Vigileo/FloTrac System to Monitor Fluid Responsiveness in Mechanically Ventilated Patients. *Anesth Analg* [Internet]. 2009 Feb [cited 2017 Jan 26];108(2):513–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19151280>
 53. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. *Crit Care Med* [Internet]. 2009 Mar [cited 2017 Jan 16];37(3):951–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19237902>
 54. Bias M, Vidil L, Sarabay P, Cottenceau V, Revel P, Sztark F. Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo/FloTrac device. *Crit Care*. 2009;13(6):R195.
 55. Monnet X, Dres M, Ferre A, Le Teuff G, Jozwiak M, Bleibtreu A, et al. Prediction of fluid responsiveness by a continuous non-invasive assessment of arterial pressure in critically ill patients: comparison with four other dynamic indices. *Br J Anaesth* [Internet]. 2012 Sep 1 [cited 2017 Jan 16];109(3):330–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22735299>
 56. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med* [Internet]. 2005 Sep 30 [cited 2017 Jan 16];31(9):1195–201. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16059723>
 57. Sandroni C, Cavallaro F, Marano C, Falcone C, De Santis P, Antonelli M. Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: a systematic review and meta-analysis. *Intensive Care Med* [Internet]. 2012 Sep 26 [cited 2017 Jan 16];38(9):1429–37. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22732902>
 58. Zimmermann M, Feibicke T, Keyl C, Prasser C, Moritz S, Graf BM, et al. Accuracy of stroke volume variation compared with pleth variability index to predict fluid responsiveness in mechanically ventilated patients undergoing major surgery. *Eur J Anaesthesiol* [Internet]. 2009 Oct [cited 2017 Jan 16];27(6):1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20035228>
 59. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med* [Internet]. 2004 Sep 25 [cited 2017 Jan 15];30(9):1834–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15045170>

60. Zhang Z, Xu X, Ye S, Xu L. Ultrasonographic Measurement of the Respiratory Variation in the Inferior Vena Cava Diameter Is Predictive of Fluid Responsiveness in Critically Ill Patients: Systematic Review and Meta-analysis. *Ultrasound Med Biol* [Internet]. 2014 May [cited 2017 Jan 16];40(5):845–53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24495437>
61. Charbonneau H, Riu B, Faron M, Mari A, Kurrek MM, Ruiz J, et al. Predicting preload responsiveness using simultaneous recordings of inferior and superior vena cavae diameters. *Crit Care* [Internet]. 2014 Sep 5 [cited 2017 Jan 16];18(5):473. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25189403>
62. Geerts BF, Aarts LPHJ, Groeneveld AB, Jansen JRC. Predicting cardiac output responses to passive leg raising by a PEEP-induced increase in central venous pressure, in cardiac surgery patients. *Br J Anaesth* [Internet]. 2011 Aug [cited 2017 Jan 15];107(2):150–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21622963>
63. Trepte CJC, Eichhorn V, Haas SA, Stahl K, Schmid F, Nitzschke R, et al. Comparison of an automated respiratory systolic variation test with dynamic preload indicators to predict fluid responsiveness after major surgery. *Br J Anaesth* [Internet]. 2013 Nov 1 [cited 2017 Jan 16];111(5):736–42. Available from: <http://bja.oxfordjournals.org/lookup/doi/10.1093/bja/aet204>
64. Biais M, Nouette-Gaulain K, Roulet S, Quinart A, Revel P, Sztark F. A Comparison of Stroke Volume Variation Measured by Vigileo™/FloTrac™ System and Aortic Doppler Echocardiography. *Anesth Analg* [Internet]. 2009 Aug [cited 2016 Nov 28];109(2):466–9. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000539-200908000-00028>
65. Hofer CK, Senn A, Weibel L, Zollinger A. Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac™ and PiCCOplus™ system. *Crit Care* [Internet]. 2008 [cited 2016 Dec 12];12. Available from: <http://ccforum.com/content/12/3/R8210.1186/cc6933>
66. Slagt C, Beute J, Hoeksema M, Malagon I, Mulder J-WR, Groeneveld JA. Cardiac output derived from arterial pressure waveform analysis without calibration vs. thermodilution in septic shock: evolving accuracy of software versions. *Eur J Anaesthesiol* [Internet]. 2010 Jan [cited 2017 Jan 29];27(6):1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20090539>
67. Mayer J, Suttner S. Cardiac output derived from arterial pressure waveform. *Curr Opin Anaesthesiol* [Internet]. 2009 Dec [cited 2017 Jan 29];22(6):804–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19773648>
68. Mayer J, Boldt J, Poland R, Peterson A, Manecke GR. Continuous Arterial Pressure Waveform–Based Cardiac Output Using the FloTrac/Vigileo: A Review and Meta-analysis. *J Cardiothorac Vasc Anesth*. 2009;23(3):401–6.

17.2 ANNEX 2: VIGILEO/FLOTRAC SYSTEM

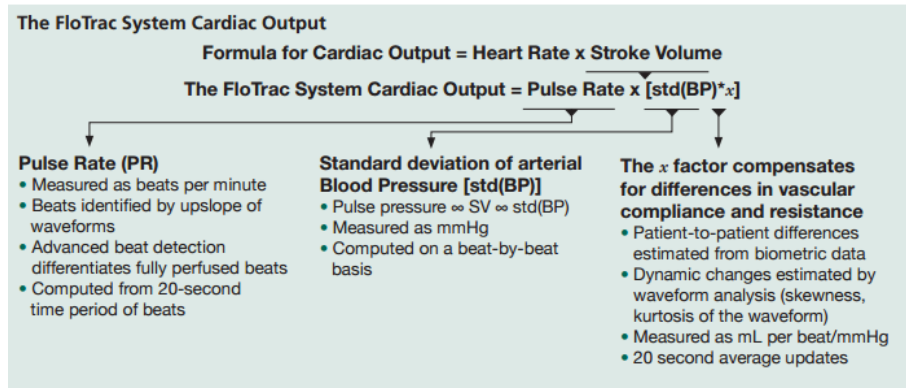


Figure 7: CO algorithm calculated with Vigileo/FloTrak system. Vigileo/FloTrac system is able to calculate CO through an algorithm based on the principle that pulse pressure is proportional to SV and is inversely related to aortic distensibility (23).



Figure 8: Edwards Vigileo system

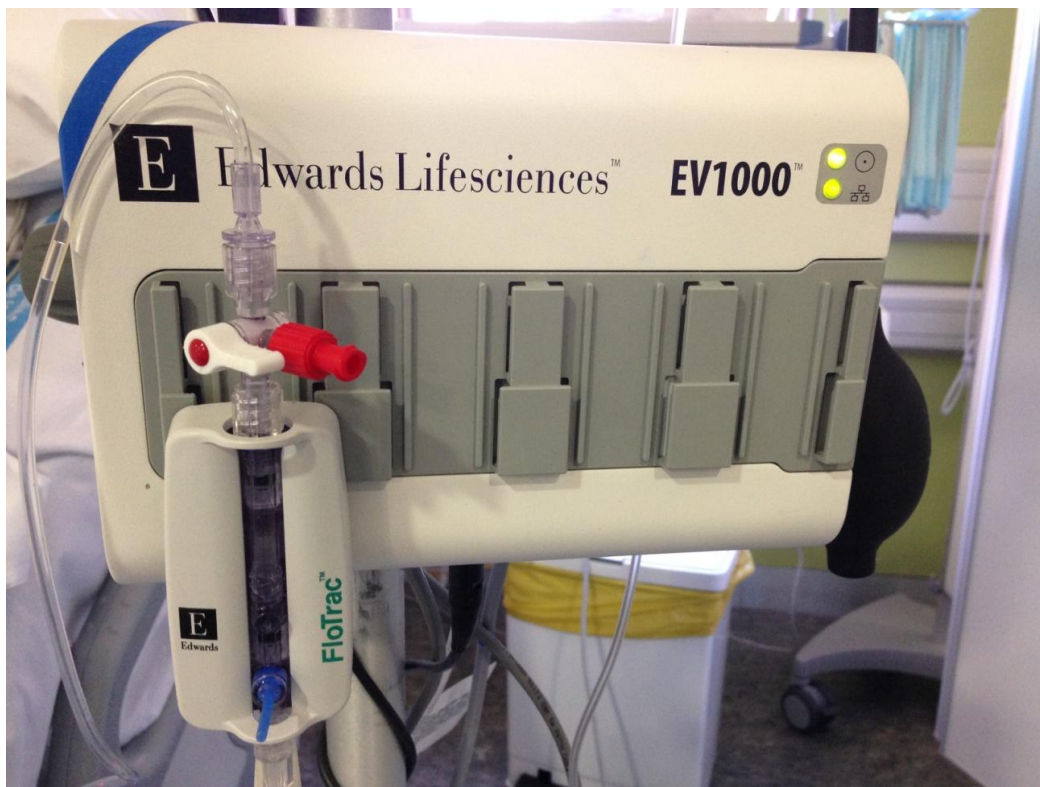


Figure 9: Edwards FloTrac system.

17.3 ANNEX 3: INFORMED CONSENT SHEET

CONSENTIMENT INFORMAT

Declaració del participant: Jo, _____ o jo,
_____ representant legal de
_____.

Declaro que:

- Entenc que la meva participació és voluntària.
- He llegit la fulla informativa sobre l'estudi que se m'ha entregat.
- He rebut suficient informació sobre l'estudi.
- He pogut fer totes les preguntes necessàries respecte l'estudi.
- He estat informat per l'investigador.....de les implicacions i finalitats de l'estudi.
- Entenc que s'adoptaran les mesures per garantir la confidencialitat de les meves dades en compliment de la Llei Orgànica 15/1999 .

▪ **Concedeixo l'ús de les meves dades o del meu representat legal per fins relacionats amb el projecte anomenat: Staggered Passive Leg Raising Test for predicting degrees of fluid responsiveness in mechanical ventilated patients.**

Firma del participant

Firma de l'investigador

Data: __/__/__

Data: __/__/__

17.4 ANNEX 4: PATIENT INFORMATION SHEET

FULL D'INFORMACIÓ PEL PARTICIPANT

INVESTIGADORS PRINCIPALS: Rosa Bernabeu Santisteban, Antonio Villalonga Morales

CODI DEL PROJECTE: _____

- 1) **Generalitats del projecte:** El present estudi observacional serà dut a terme per la unitat d'Anestesiologia i Reanimació de l'Hospital Universitari Josep Trueta de Girona, en el moment abans de la cirurgia a la que té programat sotmetre's el pacient. El projecte de recerca ha estat valorat i aprovat pel Comitè Ètic d'Investigació Clínica de l'Hospital Universitari Doctor Josep Trueta.
- 2) **Objectius i finalitats de l'estudi:** La finalitat d'aquest estudi és trobar una relació entre la prova d'elevat les cames esglaonada i els paràmetres hemodinàmics que es monitoritzen durant la cirurgia per a poder aconseguir ajustar millor la dosi de líquid que se li ha d'administrar als pacients en una situació en la que es necessiti millorar la volèmia.
- 3) **Participació:** La seva participació en l'estudi és totalment voluntària i no s'obté cap compensació econòmica. La tasca del participant, consta en facilitar l'accés i l'anàlisi de les seves dades als investigadors i permetre que en els moments previs a la cirurgia se li administri una solució electrolítica de 4mL/kg.
- 4) **Confidencialitat i protecció de dades:** S'adoptaran les mesures per garantir la confidencialitat de les seves dades en compliment de la Llei Orgànica 15/1999 i les dades recollides seran gestionades de forma anònima i només utilitzades amb fins d'investigació. També es garantiran els principis establerts per la Llei d'Investigació Biomèdica 14/2007.
- 5) **Resultats i beneficis de la investigació:** El pacient està en el seu dret de ser informat dels resultats de la investigació. Els beneficis derivats de la investigació, tan poden beneficiar al participant com a altres persones, i aquests seran adequadament utilitzats per assolir els objectius de l'estudi i serviran de base per futures investigacions en aquest àmbit.

Gràcies per la seva participació.

17.5 ANNEX 5: RESEARCHERS COMMITMENT

RESEARCHER'S COMMITMENT

Dr./Mr./Mrs. _____

Service:

Exposes:

I have evaluated the protocol of this clinical trial titled:

Staggered Passive Leg Raising Test for predicting degrees of fluid responsiveness in mechanical ventilated patients.

Referring to these aspects:

- The clinical trial respects the ethical rules relevant to these kind of studies, according to good clinical practice recommendations, in Helsinki, Declaration of World Health Organization (15 January of 2001), and to the legal normative applicable.
- I agree to participate as a researcher in this clinical trial.
- I have all the material and human resources necessary to carry on the clinical trial without affecting the performance of other studies or my usual duties.

Girona, ___/___/20__