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Functional Hemodynamic Monitoring

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Abstract

Functional hemodynamic monitoring is the assessment of the dynamic interactions of hemodynamic variables in response to a defined perturbation. Dynamic tissue O_2 saturation (StO_2) responses to complete stop flow conditions (vascular occlusion test), which can be created by measuring hand StO_2 and occluding flow with a blood pressure cuff, assesses cardiovascular sufficiency and microcirculatory blood flow distribution. Recent interest in functional hemodynamic monitoring for the bedside assessment of cardiovascular insufficiency has heightened with the documentation of its accuracy in predicting volume responsiveness using a wide variety of monitoring devices both invasive and non-invasive and across multiple patient groups and clinical conditions. Accordingly, fluid responsiveness can be predicted in a quantities fashion by measuring as arterial pulse pressure variation, left ventricular stroke volume variation or their surrogates during positive pressure breathing or the change in cardiac output response to a passive leg raising maneuver. However, volume responsiveness, though important, reflects only part of the overall spectrum of functional physiological variables that can be measured to define physiologic state and monitor response to therapy.

1. Introduction

Hemodynamic monitoring is the active assessment of cardiopulmonary status by the use of biosensors that assess physiologic outputs. The simplest form of monitoring is the health care professional themselves, inspecting the patient to see if they are conscious, agitated or in distress, breathing regular or labored, presence or absence of central and peripheral

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Potential conflicts of interest for Michael R. Pinsky, MD

- He is the inventor of a University of Pittsburgh US Patent “Use of aortic pulse pressure and flow in bedside hemodynamic management.”
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cyanosis; touching of the skin of a patient to note if it is cool and moist, and if capillary refill is rapid or not; palpation of the central and peripheral pulses to note rate and firmness.

Although well established and important as bedside diagnostic tools these simple “human instrument” measures can be greatly expanded by the use of pulse oximetry to estimate arterial oxygen saturation (SpO_2), and the sphygmomanometer and auscultation to note systolic and diastolic blood pressure and identify pulsus paradoxus. These classical measures of hemodynamics, often referred to as routine vital signs, are central to the assessment of cardiorespiratory sufficiency and much of diagnostic bedside medicine is rooted in these important techniques.

However, with some exceptions, these simple and inexpensive measures do not have the discriminatory value in identifying patients as being stable or unstable when compensatory processes mask instability or when change sin physiologic state occur rapidly. Furthermore, they predict poorly who are early on in an instability process, such as hypovolemia or heart failure, but compensating. Within the context of circulatory shock, tachycardia may or may not develop early and even if it is present, it is non-specific. However, these simple measures can be markedly helped in their sensitivity to detect effective hypovolemia by making these same measures before and during an orthostatic challenge. For example, measuring blood pressure and pulse rate changes between lying supine, sitting and standing markedly increase the diagnostic capability of the measures to identify functional hypovolemia. If heart rate increases and/or blood pressure decreases with sitting or standing, then it is reasonable to presume that some degree of hypovolemia exists consistent. However, the other important concept here in making these observations is that the measures themselves do not change, but their measured values change in response to a defined physiologic challenge. This is an example of Functional Hemodynamic Monitoring [1]. Functional Hemodynamic Monitoring is the use of a defined physiologic stressor to access the physiologic reserve of the system.

Another example of Functional Hemodynamic Monitoring is to use the morphology of the normal lead II electrocardiogram (ECG) to define ischemic heart disease. In practice, unless there is ongoing ischemia or prior infarction, the rhythm and morphology of the ECG signal is a poor marker of clinically relevant coronary artery disease. However, that same ECG signal, if monitoring during an exercise challenge that increases heart rate above some minimal amount, defined by subject age, does not show any morphologic changes or arrhythmias, then it is highly unlikely that the subject has clinical significant coronary artery disease. Importantly, as with the measure of pulse rate and blood pressure, the ECG monitoring has not changed, it is the intervention that creates evolving hemodynamic parameters that markedly increase the sensitivity and specificity of hemodynamic monitoring to define cardiovascular state.

Using Functional Hemodynamic Monitoring principles to be described below, it is possible for the bedside clinician to answer four interrelated and important questions of their patient [2]:

- Are they in compensated shock?

- Are they volume responsive?
- Is their arterial tone increased, normal or decreased?
- Is their heart able to sustain flow without high filling pressures?

Importantly, although the examples below reflect well validated approaches to address each of these clinically relevant questions, they are neither complete nor exhaustive in their number and applications. Indeed, identifying novel functional parameters to define physiologic state, be is neurological reserve, respiratory function, renal filtering or gut absorption reflect evolving frontiers of this approach across critical care disciplines. New indices of bodily functional reserve and constantly being identified and the actual number of such potential indices is vast. The major issue going forward will not be the sensitivity or specificity of any new index, since most are quite sensitive and specific, it will be the ease to which they can be assessed continuously or repeatedly and their level of invasiveness. However, those examples shown below have been proven to be robust parameters and easily used parameters of physiologic reserve and can be used as templates in validating and applying novel future indices.

2. Early identification of compensated shock

It is difficult to identify patients early on in the course of circulatory shock because normal sympathetically-medicated compensatory reflex mechanisms express themselves so as to sustain a relatively normal organ perfusion pressure and blood flow. For example, the normal response of the body to hypovolemia or impaired ventricular pump function is to attempt to maintain an adequate mean arterial pressure (MAP) by increasing sympathetic tone causing vasoconstriction, decreasing unstressed vascular volume, increased contractility and tachycardia. In a healthy athlete early on in hypovolemic shock, tachycardia may not present, and in the elderly and those with dysautonomia tachycardia may not develop at all. Since these reflex sympathetic feedback mechanisms aim to sustain MAP above some minimal value to maintain cerebral and coronary blood flow, and since vascular capacitance is reduced to sustain cardiac output, hypotension not only occurs late but must be associated with tissue hypoperfusion. Hypotension in the setting of circulator shock must also reflect failure of intrinsic compensatory mechanisms to sustain normal homeostasis. Thus, hypotension is a medical emergency not only because it must be associated with tissue hypoperfusion but also because it signals loss of intrinsic mechanisms to sustain effective blood flow. Furthermore, restoring MAP by the use of vasopressors improves tissue oxygenation in septic patients [3]. Thus, the immediate restoration of MAP while other flow-directed resuscitation efforts are underway is essential to minimize ongoing tissue hypoperfusion.

Thus, if the bedside clinician waits for the patient to develop hypotension before treating cardiovascular insufficiency then some level of organ hypoperfusion must also co-exist. Most goal directed therapy resuscitation protocols show that prevention of tissue hypoperfusion by targeted hyper resuscitation prior to developing hypovolemia is associated with improved outcomes [4]. Biosensors and maneuvers that identify occult circulatory shock will be of importance in identifying those subjects at risk for hypoperfusion before

severe tissue hypoperfusion develops. Furthermore, if their alarms trigger focused resuscitation efforts to prevent tissue hypoperfusion, improved outcome may also be realized as long as the primary cause of the hypoperfusion is also addressed. For example early identification of occult hypovolemia associated with gastrointestinal hemorrhage will allow earlier fluid resuscitation but may not improve outcome if the cause of the hemorrhage is not also addressed. However, since cardiovascular insufficiency is characterized by an inadequate O_2 delivery relative to the metabolic demands, some level of decreased cardiovascular reserve must also be present in the early stages of shock. Since progressive hypovolemia can be initially compensated by autonomic mechanisms, regional vasoconstriction should be a common characteristic of compensated or early shock prior to the development of hypotension. In this stage of compensated shock, microcirculatory O_2 use, like arterial pressure or cardiac output are often normal as the compensatory mechanism effectively sustain tissue O_2 delivery above a crisis level. However, microcirculation alterations in muscle and skin blood flow already occur in these early stages of shock because these vascular beds have high concentrations of alpha-adrenergic receptors. And resuscitation restores microcirculatory flow in a directionally similar fashion to the increases in cardiac output [5]. Thus, measures of tissue cardiovascular reserve should be a sensitive early warning measure of impending cardiovascular collapse. One method to assess the microcirculatory status is the non-invasive measurement of tissue oxygen saturation (StO_2).

2.a. Non-invasive measures of oxygen delivery sufficiency

A fundamental unanswered question in shock resuscitation is the level of tissue perfusion and tissue wellness. Resuscitation of shock patients is one of the most challenging aspects of acute care medicine in regards to determining an optimal resuscitation endpoint as patients may have inadequate regional tissue O_2 delivery despite apparent adequate systemic perfusion. Traditional endpoints of resuscitation, including targeting a minimal MAP, normalization of arterial base deficit or lactate, increased urine output, or restoration of mixed venous O_2 saturation (SvO_2) or central venous O_2 saturation ($ScvO_2$) to some minimal value carry inherent flaws in their application and their practicality. In addition, many patients who are thought to be fully resuscitated, as defined by achieving a target MAP, have markedly reduced intravascular volume, a condition known as under-resuscitated shock. If not resuscitated further, these patients develop progressive ischemic tissue injury and eventually organ failure and death. This state is commonly seen in trauma victims who initially respond to small volume fluid resuscitation but if not further resuscitated have an extremely high incidence of end-organ injury and death. If non-invasive measures of tissue O_2 delivery sufficiency could be made, then these under resuscitated patents could be readily identified and treated.

Non-invasive measurement of StO_2 using near-infrared spectroscopy (NIRS) is an accurate and valid method to assess regional tissue O_2 saturation under local sampling volume of the sensing probe. NIRS has been used to assess the adequacy of cerebral, renal and muscle blood flow by measuring local StO_2. Regrettably, absolute StO_2 values are of limited discriminating capacity because StO_2 remains within the normal range until tissue hypoperfusion is quite advanced. But the addition of a dynamic ischemic challenge and noting the local response to that challenge has proven useful in exposing early

cardiovascular stress. Although StO_2 values do not decrease until tissue perfusion is very low, this measure becomes more sensitive and specific when monitoring the change in StO_2 in response to a vascular occlusion test (VOT).

The VOT is a Functional Hemodynamic Monitoring approach to uncover problems in baseline blood flow distribution and cardiovascular reserve. The VOT StO_2 wave form is shown in figure 1 and described below. If the StO_2 probe is placed on the thenar eminence and a downstream arm blood pressure cuff is inflated to a pressure in excess of systolic arterial pressure, then one can assess the effects of total vascular occlusion-induced tissue ischemia and release on downstream StO_2. StO_2 is measured on the thenar eminence and transient rapid vascular occlusion of the arm by sphygmomanometer inflation to 20 mmHg above systolic pressure is performed either for a defined time interval, usually 3 min, or until StO_2 declines to some threshold minimal value, usually 40%. This minimal StO_2 value is presumed to induce a maximal level of local vasodilation. After which time point the vascular cuff is rapidly deflated to allow vascular reflow and wash out of the deoxygenated blood from the downstream vascular beds. Several important parameters emerge from the VOT. The StO_2 down slope or deoxygenation rate (DxO_2) reflects the local metabolic rate and effective local blood flow distribution. The StO_2 recovery or reoxygenation rate (RxO_2) reflects local cardiovascular reserve and microcirculatory flow, as validated in trauma and septic patients compared to normal volunteers [6].

2.a.i. Deoxygenation—The DeOx slope will increase if local metabolic rate increases, as will occur with contraction of the thenar muscles [6]. The DeOx slope will decrease if local metabolic rate decreases, but since it is difficult to decrease resting skeletal muscle oxygen consumption unless hypothermia exists; decreases in the DeOx slope usually reflect prior loss of vascular autoregulatory control. If prior to inducing total vascular occlusion the thenar vascular displayed a vasoplegic state, then blood flow would become more uniform thus increasing blood flow to capillary networks with a low intrinsic metabolic rate to levels similar to those beds with higher metabolic rates. The flow to the higher metabolic rate tissues would still be adequate but “wasted” perfusion would result in a higher end-capillary pO_2 than would otherwise be the case if flow were only proportional to metabolic need. On a macroscopic level this is the presumed reason for the high mixed venous O_2 saturation (SvO_2) in hyperdynamic hypotensive septic shock. Thus, following regional vascular occlusion the regional StO_2 of normally perfusion capillary beds would decrease at its normal deoxygenation rate, whereas those with excessive flow for their metabolic needs would decrease more slowly. The StO_2 probe measures a mean StO_2 for the entire bed, thus it would report a DeOx slower than would otherwise be the case. Thus, the slower the DeOx rate the presumably greater the degree of vascular paralysis.

2.a.ii. Reoxygenation—The ReOx reflects local vascular reserve. Since the occlusion causes global StO_2 to decrease to a very low value (i.e. 40%) local hypoxic vasodilation becomes maximal such that the ReOx rate will reflect only inflow rate of oxygenation blood. If vascular tone upstream from the site of vascular occlusion (usually the forearm) is increased, then despite removing the downstream occlusion the inflow of oxygenated blood will be less rapid decreasing the rate of washout or ReOx. Indeed, both a decrease in DeOx

in sepsis and a decrease in ReOx prior to fluid resuscitation have been reported in patients with septic shock.

The hypothesis that the alterations in VOT StO_2 response are related to the outcome has been proven in patients with either severe sepsis or septic shock by Creteur et al. [7]. Furthermore, when comparing to hemodynamically stable patients without infection (controls) and healthy volunteers, the septic patient differences were striking. Using the StO_2 VOT Creteur and colleagues assessed ReOx as well as by the difference between the maximum StO_2 and the StO_2 baseline as a measure of reactive hyperemia. Both, the slope of ReOx and the overshoot were significantly lower in septic patients than in controls and healthy volunteers. The DeOx slopes were also significantly lower in the septic shock patients with cardiovascular insufficiency. ReOx slopes were higher in survivors than in non-survivors and also tended to increase during resuscitation only in survivors. Finally, the ReOx slope was found to be a good predictor of ICU death. These differences between survivors and non-survivors were independent of MAP or vasopressor therapy. These data suggest that the alterations in VOT StO_2 ReOx are related more to the sepsis process itself and its severity than to organ perfusion pressure (MAP) or vasomotor tone (vasopressor therapy). If ReOx slope reflects inadequate local cardiovascular reserve then it should also sensitive of an impending cardiovascular insufficiency state (compensated shock) if matched with other static measures of tissue ischemia.

Microcirculatory failure during shock is also thought to be a major component of the associated end-organ dysfunction [8]. Such microcirculatory dysfunction can be characterized by oxygen shunting, vasoconstriction, thrombosis and tissue edema. As a result of these combined microcirculatory events, the flow distribution within the tissue is impaired. These microcirculatory alterations improve rapidly in survivors of septic shock whereas patients dying by organ failure have a lower percentage of perfused small vessels [9].

2.b. Predicting outcome from septic shock

Mesquida et al. [10] took this approach one step further and explored the StO_2 VOT was a predictor of tissue hypoperfusion and organ injury using the SOFA score as a maker of organ injury. They studied 33 patients with septic shock following restoration of MAP. Baseline StO_2 was 76±1-% and were not different from values reported for normal controls. Interestingly, MAP correlated with both DeOx and ReOx slopes consistent with known better tissue perfusion associated with high MAP in septic patients. However, after 24h, only 17 patients had improved SOFA scores, consistent with improved organ system function. Whereas those 18 other patients who did not demonstrate improved SOFA scores showed a persistently flattened DeOx slope consistent with persistent vasoplegia, and both DeOx and ReOx slopes impairments correlated with longer ICU stays. Thus, by using a simple VOT, the NIRS StO_2 measure creates DeOx and ReOx parameters defining effective tissue blood flow.

2.c. Predicting need for Life-Saving Interventions

Perhaps more convincingly, Guyette et al. showed that the StO_2 DeOx was able to predict the subsequent need for Life Saving Interventions (LSI) in STAT MedEvac air transport of trauma patients being transported to a level 1 trauma center [11]. They assessed the predictive value of lactate and the StO_2 VOT in trauma patients during emergency air transport into the hospital from an accident site, usually a motor vehicle accident. All patients were monitored using 3-lead ECG, non-invasive blood pressure, heart rate, pulse oximeter O_2 saturation (SpO_2), and when intubated, end-tidal CO_2 capnography. Previous work has documented that these single vital signs are not sensitive at identifying shock until advanced [12]. Since protocol-based algorithms typically rely on individual vital signs or clinical parameters (i.e. cyanosis, altered mental status) to identify the need for LSI [13,14] and having robust parameters of impending instability are important for the acute care triage of this salvageable critically ill trauma patients. Subjective measures such as acute changes in mental status may be used to identify hemorrhagic shock but are difficult to standardize and vary based on the provider's skill and experience [15].

Guyette and colleagues hypothesized that in-flight measures of serum lactate and StO_2 VOT would identify shock trauma subjects in need of LSI [16,17]. They studied 400 transported trauma patients with lactate sampling and 194 patients also with StO_2 VOT. The aim of the study was to see if the StO_2 measurement, including a VOT, and spot measures of serum lactate were feasible in the prehospital air transport environment and useful to predict in-hospital death and intensive care unit (ICU) admission. Patients with pre-hospital lactate levels >4 mmol/dl had greater need for emergent operation, intubation, and vasopressors. This association persisted after adjustment for age, Glasgow Coma Score and initial vital signs. Not surprisingly, they did not find differences in baseline StO_2 between survivors, non-survivors and patients admitted to the ICU. However, they found significant differences in DeOx and ReOx slopes between survivors and non survivors, as well as between patients who need ICU admission and patients who did not. The StO_2VOT DeOx slopes were predictive of the need for LSI, while a delayed ReOx slope was predictive of mortality (Table 1). Furthermore, only one of the five patient deaths in their sample had prehospital vital signs that would have met the protocolized criteria for resuscitation (heart rate >120 bpm, systolic blood pressure < 90 mmHg). Importantly, serum lactate alone was no better than lowest systolic pressure in predicting those in need of LSI or death, but if the baseline serum lactate was >1.7 mmol/dl the ReOx slope was 100% specific for the need of LSI. This study shows the usefulness of the microcirculation dynamic assessment in the early stages of the trauma injury, when the cardiovascular insufficiency is not suspected based solely on macrocirculatory indexes.

Thus, using a Functional Hemodynamic Monitoring approach, measures of StO_2 may provide the possibility to start earlier the appropriate treatment and decide the in-hospital disposition. These data collectively document that the measure of readily available physiological variables when coupled to Functional Hemodynamic Monitoring principles (e.g. VOT) predict clinically relevant physiological states and the subsequent need for LSI.

Although we have focused on StO_2 and its changes during a VOT, other potential Functional Hemodynamic Monitoring applications must exist and should be useful in

identifying impeding cardiovascular instability and its response to therapy. However, a fundamental aspect of these novel monitoring devices will probably be their non-invasive nature allowing widespread use with minimal risk, continuous in their measures, allowing trending of state, and metabolic ion their orientation, because assessment of tissue wellness and metabolic status is central to defining the severity of circulatory shock.

3. Predicting Volume Responsiveness

A fundamental aspect of the initial resuscitation of a patient in circulatory shock is to restore MAP and global blood flow as soon as possible as to minimize tissue hypoperfusion, organ injury and subsequent inflammatory responses. Given the caveat that in traumatic injury acquiring surgical control of large vascular injuries prior to large volume resuscitation, all other forms of resuscitation presumes a hypovolemic intravascular state in need of immediate fluid resuscitation. Clearly, for the resuscitated patient presenting to the Emergency Department after a prolonged and progressive deterioration from slow hemorrhage, severe diarrhea and infection, profound hypovolemia is almost universally present and requiring of intravascular fluid repletion. However, many patients present with pre-existing cardiovascular conditions, such as heart failure, chronic obstructive pulmonary disease, diabetes, and essential hypertension, all of which limit the ability of fluid resuscitation to universally augment cardiac output. Similarly, patients already hospitalized who acutely decompensate, either form occult bleed or sepsis may not present in a state of absolute hypovolemia.

Thus, it is not surprising that Michard and Teboul, when reviewing all the reported studies giving fluids as the initial management of circulatory shock found that half the patients did not increase either cardiac output or blood pressure [18]. They refer to those patients who in shock who do not respond favorably to an initial fluid bolus as preload non-responders. These data suggest that as many as half of all hemodynamically unstable patients are not preload responsive and that the blind use of fluid resuscitation as the initial management of all patients presenting in circulatory shock will be ineffective half the time. Furthermore, fluid resuscitation has adverse effects, such a venous pressure overload promoting pulmonary and peripheral edema, acute cor pulmonale and cerebral edema. Therefore, using clinically reliable parameters that identify patients who will respond to volume expansion helps to avoid potential harm to non-responders of inappropriate fluid resuscitation.

Since a primary resuscitation question when addressing management of the hemodynamically unstable patient is whether or not the patient will increase their cardiac output in response to intravascular volume infusion, knowing the volume responsiveness state is clinically important. Volume responsiveness has been arbitrarily defined as a ≥15% in cardiac output in response to a 500 ml bolus fluid challenge. Although the presence of fluid responsiveness in a subject does not equate for the need to give fluids, it does define that if fluids are infused cardiac output will increase.

3.a. Static preload measures do not predict preload responsiveness

Cardiac preload is the maximum degree of myocardial fiber stretch or tension prior to ventricular contraction. When fibers are part of the ventricular wall they form hoops such

that ventricular end-diastolic volume (EDV) is usually proportional to fiber stretch. Thus, ventricular EDV is usually used as a measure of preload. Measures of ventricular filling pressures estimate which is are presumed to reflect ventricular preload. Based on this knowledge bedside clinicians seek surrogate measures of preload to guide resuscitation therapies. Unfortunately, this LV volume-stretch relation is commonly altered by myocardial ischemia and ventricular interdependence. In both cases LV diastolic compliance decreases, such that for the same EDV as diastolic compliance decreases wall stretch must increase. This is the reason why changes in LV stroke volume, as a surrogate for changes in LV preload, become unreliable during spontaneous breathing, as will be described below when dynamic indices of volume responsiveness remain predictive.

Common clinical teaching dictates that static hemodynamic measures, such as central venous pressure (CVP), as an estimate of right ventricular (RV) filling, and pulmonary artery occlusion pressure (Ppao), as an estimate of LV filling, can be used to predict fluid responsiveness. The argument being that is CVP or Ppao are low then the subject will be volume responsive and if either is elevated, the subject will not. However, this presumption has never been rigorously validated and indeed is probably incorrect over the range of pressures commonly seen in critically ill patients. Recent clinical trials and large meta-analyses of pooled studies show that static measures of either RV or LV preload do not identify those patients who will increase their cardiac output in response to fluid loading [19-24]. The reasons for this lack of clinical utility may include errors in measurement, lack of physiologic rationale and misinterpretation of the meaning of the measures themselves. Since mechanical ventilation and spontaneous breathing often influence static measures made at the bedside differently and the physiological interactions between heart and lung vary between these two forms of breathing we shall explore each separately.

3.a.i. Estimates of preload during positive-pressure ventilation—Mechanical ventilation has a significant effect on cardiovascular function which depends on the baseline contractility and intravascular volume status, chest wall and lung compliance, tidal volume and ventilatory pattern [25]. Importantly, positive-pressure breathing cyclically increases in intrathoracic pressure (ITP) by forcing the expanding lungs to passively expand the chest wall. This causes CVP to increase proportionally. Since CVP is the backpressure to systemic venous return to the heart, these cyclic increases in CVP cause reciprocal cyclic decreases in venous return. End-expiratory CVP is often taken as an estimate of the intravascular state. A low CVP (<8 mmHg) is presumed to reflect a low circulating blood volume and a high CVP an expanded blood volume [26,27]. Regrettably, neither CVP nor Ppao predict a patient's response to fluid challenges [28-30]. By meta-analysis CVP was found to have a very poor correlation with subsequent increases in cardiac output in response to a fluid challenge (r=0.18) with no discriminating power [31] Still, CVP does have usefulness in predicting if increasing the level of positive end-expiratory pressure (PEEP) will result in a decrease in cardiac output or not. Jellenik et al. examined the relation between baseline CVP and the subsequent change in cardiac output in response to a 10 cm H_2O increase in PEEP from 0-10, 10-20 and 20-30 cmH_2O in 22 consecutive ventilator-dependent patients with acute respiratory distress syndrome [32]. They found that at all times, if the initial CVP was ≤8 mmHg cardiac output invariably decreased, whereas the change in cardiac output if CVP

was >8 mmHg was not predictable. Accordingly, identifying ventilator-dependent patients with a low CVP (≤8 mmHg) defines a subgroup of critically ill patients at risk for decreasing cardiac output if PEEP levels are increased.

CVP can be estimated non-invasively by measuring inferior vena caval (IVC) diameter by ultrasound techniques using the sub-xiphoid window. IVC diameters <12 mm were predictive of volume response while values >20 mm predicted non-responders, with values in the middle not predictive at all [20]. Within this context, respiratory changes in IVC diameter may be helpful in predicting fluid response in mechanically ventilated patients as a Functional Hemodynamic Monitoring approach. In a study of septic patients, inspiration-associated IVC diameter decreases >50% correlated with a CVP <8 mmHg (r=0.74) [33]. Since CVP <8 mmHg defines the subset of patients who will decrease their cardiac output in response to increasing PEEP, this finding is clinically relevant.

Similarly cardiac ultrasound can be used to identify the presence or absence tricuspid regurgitant jets. The greater the degree of tricuspid regurgitation, the higher the estimated pulmonary artery pressure, although this measure can be inaccurate at higher pulmonary arterial pressures.

Another static measure of preload is global EDV index (GEDVi), the summed volume of all four chambers of the heart, estimated by pulmonary artery to transthoracic indicator dilution transit time differences. Not surprisingly, 80% of volume responders have GEDVi I <600ml/m^2 while only 30% of patients with a GEDVi >800ml/m^2 are volume responders [34]. However, like IVC diameter ranges, GEDVi in the intermediate range between these two extremes does not distinguish volume responders from non-responders. Theoretically, RV EDV should be a good measure of preload. Still, resuscitation efforts adding measures of GEDVi to their resuscitation algorithms allowed caregivers to choose between volume, red cell transfusion and vasopressors in the management of critically ill patients [35]. So the use of GEDVi is not without value when used within a treatment algorithm. Another static measure obtained from the pulmonary artery thermodilution technique is the RV EDV index. Similar to the GEDVi data, RV EDV values <90 ml/m^2 predict volume responders while RVEDV values >140 ml/m^2 predict volume nonresponders, whereas intermediate RV EDV values do not distinguish volume responders from non-responders [36].

Transthoracic and transesophageal echocardiography can reliably measure ventricular enddiastolic area. However, measures of end-diastolic area are also poor predictors of volume response. Still, these measures have a one-way decimatory value. If the ratio of RV enddiastolic area to LV end-diastolic area is >1, such patients are presumed to have cor pulmonale, a conditions for which volume resuscitation is contraindication even in the setting of circulatory shock because as the right ventricle dilates further with volume loading, LV EDV progressively decreases further worsening the low output shock state [37].

3.b.ii. Estimates of preload during spontaneous breathing—Static estimates of preload are not much better at predicting volume responsiveness during spontaneous ventilation. In general, like with positive-pressure ventilation, they are predictive at the extremes of very low/small and very high/large measures but not predictive over a range

normally seen in most critically ill patients at the start of resuscitation. Most studies primarily report on patients requiring mechanical ventilation, owing to the nature of critical illness and the cohort routinely instrumented with intravascular catheter. However, two studies of critically ill patients included a small subset of non-ventilated patients [38,39]. Both showed, not surprisingly that a lower initial CVP was more common in volume responders than non-responders. Though the CVP measures in these studies varied and the sample sizes were small, a low CVP (<5 mmHg) identified volume responders.

The predictive value of Ppao in spontaneously breathing patients has, in general, not been described but when reported is very poor [40]. However, one study where 6% of the study population were spontaneously breathing patients, reported that patients with a low baseline Ppao (<10 mmHg) were volume response [38]. Since the use of a pulmonary artery catheter is uncommon in spontaneously breathing patients, this observation is of little practical relevance.

Using echocardiography to estimate of RV and LV end-diastolic area, as surrogates for EDV, two studies examined the relation between RV end-diastolic index (RVEDVi) and volume responsiveness. The findings mirrored those for GEDVi and RV EDV reported above. Subjects with increased RVEDVi (>140ml/m^2) were not volume responsive, whereas those with reduced RVEDVi (<90ml/m^2) were volume responsive. Again, patients with RVEDVi between these two extremes displayed no value of RVEDVi in predicting volume responsiveness [36,41]. Similar to the lack of discrimination using Ppao to identify volume responsiveness, LV end-diastolic area also did not discriminate between volume responders and non-responders [42].

3.b. Dynamic parameters predict preload responsiveness

Dynamic changes in hemodynamic variables, such as ventilation-induced changes in CVP, arterial pulse pressure, LV stroke volume and both IVC and superior vena caval diameter have been shown to be highly predictive of volume responsiveness in a variety of clinical scenarios. The principles behind the expression of these dynamic variables is the effect of positive-pressure and spontaneous ventilation on systemic venous return and subsequently LV output. We described in great detail these interactions elsewhere [43]. In essence, cyclic increases in ITP induced by positive-pressure breathing lung expansion also increase CVP. Since CVP is the back pressure to blood flowing back to the right ventricle form the body, referred to as venous return, if the upstream pressure does not also change then with every positive-pressure inspiration, venous return will phasically decrease. If both ventricles are volume responsive, then eventually LV stroke volume must also vary, the magnitude of this variation reflecting the degree of volume responsiveness.

3.b.i. Dynamic parameters in mechanically ventilated patients—Many studies have validated the usefulness of dynamic change sin arterial pulse pressure and LV stroke volume during positive pressure breathing to predict with a high degree of accuracy if a patient is going to increase cardiac output, mean arterial pressure or both to response to the volume infusion. Some of the most commonly used Functional Hemodynamic Monitoring methods are those based in beat-to-beat changes in LV output during positive-pressure

ventilation, such pulse pressure variation (PPV) and stroke volume variation (SVV). The physiological basis for this predictive accuracy has been well described previously [44]. Briefly, during the inspiratory phase of positive pressure ventilation, ITP increases passively increasing right atrial pressure causing venous return to decrease, decreasing right ventricular output, and after two or three heart beats, left ventricular output if both ventricles are volume responsive [44]. Thus, in preload dependent patients cyclic changes in LV stroke volume and its coupled arterial pulse pressure will be seen and the magnitude of the changes is proportional to volume responsiveness.

However, there are many potential complicating processes that can lead to either false positives or false negatives when either PPV or SVV are measured. Thus, by understanding the physiological basis for the generation of PPV and SVV aids in minimizing errors in their interpretation. The positive-pressure breath generated by mechanical ventilation causes cyclic increases in ITP which simultaneously increases CVP, the back pressure to venous return. This causes RV filling to immediately decrease because venous return to the right ventricle transiently decreases. Thus, if the right ventricular is volume responsive then RV stroke volume will also decrease on the next beat. After two to three beats this decreased pulmonary arterial inflow reaches the left ventricle decreasing LV EDV. If the left ventricle is volume responsive then this decreased LV flow will result in a decreased LV stroke volume. Since it takes about three beats for the decreased RV flow to cause a decreased LV flow the observed decreased LV stroke volume seen during positive-pressure ventilation usually occurs at the start of expiration. Thus, if both the ventricles are preload responsive, then positive-pressure breaths will induce dynamic changes in LV stroke volume. Since the primary determinant of arterial pulse pressure (the increase from diastolic to systolic pressure) is stroke volume from one heart beat to the next, changes in arterial pulse pressure will also follow changes in LV stroke volume. Michard et al. [44] quantified the arterial PPV and the ratio of the difference between the maximal and the minimal pulse pressure over three breaths and the mean pulse pressure over those same breaths, reported as a percent. They demonstrated that the greater the PPV the more the subject was volume responsive. SVV is similarly quantified as the ratio of difference between the largest and smallest LV stroke volumes to the mean LV stroke volume averaged over 3-5 breaths (Fig. 3). Newer arterial waveform monitoring devices estimate LV stroke volume on a beat-to-beat basis allowing continuous reporting of both PPV and SVV. Commercially-available devices include PiCCO (Pulsion Ltd), LiDCO (LiDCO Ltd), Vigileo (Edwards Lifesciences), MostCare, NICOM (Cheetah Medical) and others. The associated SVV and PPV are quantified in various ways depending on whether these are measured by minimally invasive cardiac output monitors (e.g. PiCCO, LiDCO, FloTrac) or by direct examination of the pressure or flow profiles. In general both are defined as the ratio of the maximal minus the minimal values to the mean values, usually averaged over 3 or more breaths although one device (FloTrac) estimates SVV as the standard deviation of the pressure power signal to the mean power. Many commercially-available minimally invasive hemodynamic monitoring devices can estimate LV stroke volume from the arterial pressure profile giving similar SVV measures.

Several clinical trials have documented that a SVV >10% or a PPV >13-15% on a tidal volume of ≥8 ml/kg or greater is highly predictive of volume responsiveness [45,46,47].

When PPV was compared to CVP and Ppao in tracking the changes in blood volume in subjects undergoing acute normovolemic hemodilution, the change in PPV was more specific than were changes in CVP or Ppao [20]. While PPV has a strong predictive value, a recent study has demonstrated that values between 9-13% are inconclusive in patients undergoing general anesthesia [48]. Heijman et al. examined the discriminative value of SVV compared to static estimates of preload in predicting volume responsiveness in ICU patients after undergoing cardiac surgery [49]. They found that SVV was a better functional marker of fluid responsiveness than either CVP or Ppao. Thus, if the clinician is concerned about excess fluid administration, then targeting a higher PPV or SVV, say 20% would markedly increase the positive predictive value of these parameters in defining preload responsiveness. Although SVV should be an accurate predictor of preload responsiveness, it is usually estimated from the arterial pulse profile, thus its accuracy by be less if the algorithm used to calculate SVV is flawed or extraneous conditions arise that make the primary assumptions questionable.

3.b.i.a. Limitations to the use of dynamic parameters to assess volume responsiveness: Limitations to the use of positive-pressure induced PPV and SVV to predict volume responsiveness are listed in Table 2. One problem with measuring PPV and SVV is that it requires the positive pressure breath to generate a sufficient change in ITP to cause a physiological variation in venous return. In most studies a tidal volume of 8 ml/kg was used. Thus, tidal volumes of ≤6 ml/kg or the imposition of variable spontaneous inspiratory efforts often result in false negative PPV and SVV values [50]. Still, if one has a PPV >12% on a tidal volume of 6 ml/kg the patient is still volume responsive [51]. Moreover, all these techniques assume a fixed heart rate, so in the setting of atrial fibrillation or frequent premature ventricular contractions, these measures become inaccurate. In these settings alternative approaches to PPV and SVV can be employed while still using the same Functional Hemodynamic Monitoring logic.

A major problem is using PPV or SVV is the need for a constant R-R interval (constant heart rate) so that diastolic filling time is not contributing to the preload effect of the positive-pressure breath. Thus, in patients with frequent premature ventricular contractions or atrial fibrillation, the accuracy of these parameters degrades markedly.

Another problem with the use of PPV and SVV to predict fluid responsiveness is its false positive rate in the setting of right heart failure. With acute cor pulmonale, positive-pressure inspiration decreases RV EDV making the left ventricle more compliant, increasing LV EDV and LV stroke volume even though RV failure limits fluid responsiveness. Thus, in the setting of right heart failure, PPV and SVV may be misleading. In that regard, both PPV and SVV were examined as predictors of volume responsiveness in patients with RV failure. While increases of CVP, SVV and PPV were suggestive of RV failure, SVV and PPV failed to predict volume responsiveness in these patients [52]. Thus, caution needs to be exercised in interpreting PPV and SVV in patients with RV failure.

Intra-abdominal hypertension also invalidates the use of PPV and SVV in that a patient may remain volume responsive even if their PPV is <15% and their SVV <10%. This is because in the setting of intra-abdominal hypertension, as the diaphragm descends during the

positive pressure breath, intra-abdominal pressure increases almost as much as ITP, thus no decrease in pressure gradients for venous return are created.

3.b.i.b. Alternative dynamic measures to PPV and SVV: Alternatives to PPV measures can be assessed using similar Functional Hemodynamic Monitoring principles. Monnet et al. examined the effect of a 15-s end-expiratory pause on the change in arterial pulse pressure to predict fluid responsiveness. They reasoned that the end-expiratory pause would allow venous return to increase causing an increase in arterial pulse pressure as compared to positive-pressure breathing. In 34 patients under mechanical ventilation, a 15±15% arterial pulse pressure increase correlated with a 12±11% cardiac index increase [53].

3.b.1.c. Alternative measures to pulse pressure or LV stroke volume: As described above, ultrasound measures of IVC diameter reflect estimates of preload and respiratory variations in IVC diameter also predict volume responsiveness in ventilated patients. During positive-pressure inspiration, the increased ITP transmits to the right atrium reducing venous return causing IVC dilation, whereas during expiration, the decreased ITP increases venous return and decreases IVC diameter. Presumably the dynamic change sin IVC diameter will be greater the more volume responsive a subject is. In support of this assumption, studies in septic patients demonstrated that changes in IVC diameter >12% or IVC collapsibility index ≥18% differentiated volume responders from non-responders [54,55]. Similarly, superior vena caval (SVC) diameter change can be used. A SVC collapsibility index >36% has similar sensitivity and sensitivity in identifying volume responders as does the IVC collapsibility index [52,56,57]. However, SVC imaging can only reliably be done using transesophageal echocardiography. Since newer continuous transesophageal echocardiographic approaches have been introduced (hTEE, IMACOR) the use of the SVC collapsibility index has increased in popularity [58].

Besides SVV, PPV and IVC collapsibility index measures, there are other dynamic parameters based on the same physiologic mechanisms. Unfortunately, these other indirect measures are less predictive than SVV and PPV. These other parameters derived from arterial pressure analysis include systolic pressure variation (SPV), aortic blood flow velocity recorded via esophageal Doppler ultrasound [59,60], pressure wave variation by pulse oximetry, aortic flow velocity time [61,62] and brachial flow variation time [63]. Interestingly, plethysmographic wave via pulse oximetry (Pplet) is a non-invasive dynamic parameter that mirrors arterial pulse pressure. In mechanically ventilated patients studies have shown a good correlation between PPV and Pplet [64]. However, in the setting of spontaneously breathing patients, there's a lack of agreement on Pplet's ability to predict volume response. Since Pplet can be readily measured in any patient with a finger pulse oximeter, the potential application of this approach needs to be further studied.

3.b.1.d. Passive leg raising (PLR) maneuver: A classic method for assessing volume responsiveness in general is to note the transient effects of a passive leg raising maneuver on cardiac output and its surrogate markers. This is an especially useful approach to identifying volume responsiveness in patients with arrhythmias and/or spontaneous breathing. The PLR maneuver is performed by passively raising both legs to an angle of 45° with respect to the bed for at least one minute while continuously measuring cardiac output. The PLR

maneuver is equivalent to giving a 70 kg patient a transient volume bolus of 300 ml [65]. This maneuver essentially transfers blood from the lower extremities to the intrathoracic vessels causing an increase in intrathoracic blood volume. If the subject is volume responsive, then the PLR will increase cardiac output by at least 10% [66,67]. In the critically ill patient, raising the legs may cause pain and discomfort. A more gentle method of accomplishing the same effect is to rotate the bed from a semi-recumbent position to a supine one and hold it there for 3 minutes. Usually patients requiring mechanical ventilation are placed in a semi-recumbent position with the head of the bed elevated 30-45°. Thus, by just rotating the bed so the back is supine will elevate the legs 30-45°. Marik et al. showed that the change in cardiac output in response to PLR as measured completely non-invasively using bioreactance alone [68] and when combined with and Doppler ultrasound also predicted volume responsiveness in critically ill patients [69]. Since this PLR maneuver is temporary, it only identifies those subjects who are volume responsive, it is not a therapy into itself. The Pplet density change can also be used as a surrogate for arterial pulse pressure changes in response to a PLR to predict fluid response in Emergency Department subjects [70]. Unfortunately, the follow up study two years later by the same Emergency Department group, using the same PLR maneuver found no correlation between changes in Pplet during the PLR maneuver and subsequent changes in cardiac index in response to fluid challenge [71]. Thus, it is unclear if Pplet can be used as a surrogate for arterial pulse pressure across volume challenge tests. Potentially, the poorer performance of the Pplet parameter in the follow up paper may have been due to their studying patients following abdominal surgery. Because of the associated increased intra-abdominal pressure altering fluid shifts, PLR maneuvers cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension [72].

3.b.2. Dynamic parameters in spontaneous breathing patients—Essentially, with spontaneous inspiratory efforts ITP decreases owing to the opposing effects of lung parenchymal stiffness resisting expansion and chest wall/diaphragm contraction increasing thoracic compartment volume. The right atrial wall is highly compliant, thus all the decrease in ITP is transferred to the right atrial cavity decreasing right atrial pressure or CVP. Since CVP is the back pressure to venous return, decreases in CVP will accelerate venous blood flow back to the heart during spontaneous inspiration. If the right ventricle is volume responsive, its filling pressure will increase less than the decrease in ITP. Thus CVP will decrease during spontaneous inspiration in patients who are volume responsive. If the right ventricle is not volume response then the initial acceleration of venous return will dilate the right ventricle increasing RV end-diastolic pressure and CVP. Such spontaneous inspiration-associated increase in CVP is called Kussmual's sign and reflects cor pulmonale or tamponade [73]. In any case, patients with Kussmual's sign are not volume responsive. Importantly, the associated changes in LV EDV are not preload dependent but due to changes in LV diastolic compliance owning to ventricular interdependence.

3.b.2.a. Dynamic changes in CVP: Using the dynamic changes in CVP during spontaneous ventilation, Magder et al. predicted that those patents breathing spontaneously who displayed a decrease in CVP of >1 mmHg would be volume responsive, whereas those who did not would not be volume responsive [74]. They found that in 33 ICU patients, 12 of

which were breathing spontaneously a CVP decrease >1 mmHg predicted volume responsiveness in 13 of 14 positive patients and predicted non-responsiveness in 16 or 19 other patients. Although simple, this approach is seldom used because of the inherent difficulty in identify small changes in CVP apart from those caused by the normal cardiac cycle.

Spontaneous inspiration decreases ITP and CVP, causing venous return to accelerate, increasing RV EDV. The sudden increase in RV EDV decreases LV diastolic compliance by the process of ventricular interdependence. Thus, for the same LV filling pressure LV EDV decreases. Since preload is LV wall stress not volume, if diastolic compliance decreases then for the same filling pressure LV EDV will also decrease but LV wall stress will remain constant. Thus, LV stroke volume will change even though preload has not. Thus, during spontaneous ventilation, only right sided changes in ventricular function assessed by dynamic swings in CVP can be presumed to reflect dynamic changes in preload [75]. Whereas PPV and SVV, if present, may reflect ventricular interdependence rather than volume responsiveness.

3.b.2.b. Use of the Valsalva Maneuver to assess volume responsiveness: The most commonly studied dynamic parameter of volume responsiveness during spontaneous ventilation is the associated change in arterial pulse pressure and systolic pressure associated with the various phases of a Valsalva maneuver. The Valsalva maneuver is traditionally divided into three phases: the initial strain, the sustained strain, the immediate release and the reactive overshoot. During the initial strain of a Valsalva maneuver, airway pressure and ITP increase equally because lung volume is held constant by the occluded airway. Thus, pulmonary vascular resistance remains constant. During this first phase of the Valsalva maneuver, RV filling decreases because venous return decreases with no immediate change in LV filling, LV stroke volume, or arterial pulse pressure. Although LV stroke volume does not change, LV peak ejection pressure increases equal to the amount of the increase in ITP [76]. Thus, systolic arterial pressure increases but pulse pressure remains constant. As the strain is sustained, both LV filling and cardiac output both decrease owing to the decrease in venous return [77], which results in the second phase. During this second phase of the Valsalva maneuver, both RV and LV output are decreased. This is reflected in a decreased arterial pulse pressure. However, since ITP remains elevated mean arterial pressure is also maintained. With release of the strain in phase three of the Valsalva maneuver, arterial pressure abruptly declines as the low LV stroke volume cannot sustain an adequate ejection pressure on its own. But at the same time, with the release of the increased ITP, venous return increases, increasing RV volume, and, through the process of ventricular interdependence, decreases LV diastolic compliance, making LV end-diastolic volume even less. Thus, mean arterial pressure rapidly decreases owing to the loss of the ITP stent and a lowering LV end-diastolic volume (Fig 2). Under normal conditions a phase four hyperdynamic rebound occurs increasing both peak systolic pressure and arterial pulse pressure. This arterial pressure “overshoot” identifies adequate cardiovascular reserve. Lack of an increase in pulse pressure, connoted as the “Square Wave” response on release identifies those patients with impaired ventricular pump function [78,79]. Recently these phases were assessed by the associated arterial pulse pressure variation across phases as

opposed to across breaths, here defined as the greatest difference in arterial pulse pressure between minimal and maximal beats over the Valsalva maneuver. Using this approach Monge et al. found that a Valsalva PPV >52% predicted a positive response to fluid administration with a 91% sensitivity and 95% respectively [62].

3.b.3. Both mechanically ventilated and spontaneous breathing—One can examine the increase in arterial pulse pressure with end expiratory pause in patients spontaneously triggering positive pressure breaths while on mechanical ventilatory support, such as pressure-support ventilation, as described above for positive-pressure breathing [53]. In this case, however, threshold values of 20% for both PPV and SVV are needed to be predictive of volume responsiveness.

3.c. Limitations to predicting volume responsiveness

Volume responsiveness has been arbitrarily defined as >15% increase in cardiac output as a response to a 500 ml fluid challenge. However, these cutoff values for increase in flow and volume administered are both arbitrary and misleading. Clearly, the responses are linear and the amount of volume given should be relative to the presumed effective blood volume, a value dependent of patient size, age and sex. Similarly, some volume responsive patients may increase their MAP more than their cardiac output, whose own increase in cardiac output may be below the threshold for measurement. It is not clear if small increases in cardiac output in the management of patients at risk for tissue hypoperfusion reduce morbidity and mortality but any such treatment must be balanced by the concern for fluid overload. Thus, continuing to fluid resuscitate patients until they are no longer volume responsive will markedly over resuscitate those patients with a normal ventricular response.

Although, the presence of fluid responsiveness does not necessarily mean need for fluid resuscitation nor does it guarantee that it fluids are given to increase cardiac output that the increase in blood flow will reverse tissue hypoperfusion [80]. In mechanically ventilated patients, the major limitations are the inherent dependence on ventilator-induced changes in intrathoracic pressure great enough to change CVP. Therefore, as listed in table 2, tidal volumes <6 ml/kg or irregular spontaneous respirations will give false positive PPV and SVV. Furthermore, these dynamic measures rely on heart rate regularity; therefore arrhythmias such as atrial fibrillation can render these measures inaccurate. However, the cardiac output response to PLR will perform well in the setting of arrhythmias [59].

Finally, defining volume responsiveness by giving small volumes of fluid is not the same as fluid resuscitation. Both small fluid bolus challenges and PLR merely document volume responsiveness. Aggressive fluid resuscitation in volume responsive patients in shock improves outcome [81]. Thus, though it may be more efficient to use end points of fluid therapy based on the disappearance of preload responsiveness rather than static values of preload in guiding fluid therapy in critically ill patients in shock, a more reasonable approach would be to determine when resuscitation has reversed measures of organ and tissue hypoperfusion [82].

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Key Points

- Functional Hemodynamic monitoring reflects is the assessment of the dynamic interactions of hemodynamic variables in response to a defined perturbation.
- Dynamic tissue O_2 saturation (StO_2) responses to complete stop flow conditions (vascular occlusion test), assesses cardiovascular sufficiency and microcirculatory blood flow distribution.
- Dynamic inspiratory changes in central venous pressure (CVP) during spontaneous ventilation identify both cor pulmonale and volume responsiveness.
- Dynamic changes in arterial pulse pressure (diastole to systole) and left ventricular (LV) stroke volume during positive-pressure ventilation reflect the degree the subject is volume responsive.
- Both PPV and SVV quantitatively track volume responsiveness with a threshold value of >10-15% as defining a subject whose cardiac output will increase by >15% in response to a 500 ml fluid bolus.
- Dynamic change sin PPV and SVV cannot be used in the setting of atrial; fibrillation, acute cor pulmonale or when spontaneous breathing is forceful and erratic.
- Dynamic changes in cardiac output in response to a passive leg raising maneuver also predict volume responsiveness.
- The PPV/SVV defines central arterial stiffness or elastance and can be used as a surrogate marker of vasomotor tone.

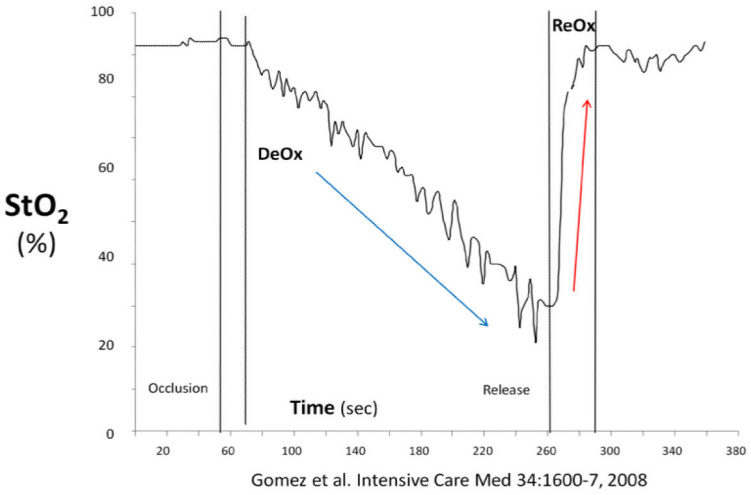

Figure 1.

Stylized display of the raw tissue oxygen saturation (StO_2) trand during a vascular occlusion test. The initial vertical line connotes the start of vascular occlusion whereas the second vertical line identified when StO_2 starts to decrease. The rate of decrease in StO_2 or deoxygenation rate (DeOx) is defined by the mean slope of the initial decrease in StO_2 following vascular occlusion (blue arrow). The third vertical line defined the point when the vascular occluder is released and forearm blood flow is resumes. The wash out of deoxygenated blood causing reoxygenation (ReOx) is the second slope of the text (red arrow). Modified from Gomez et al. Intensive Care Med 2008, 34:1600-7.

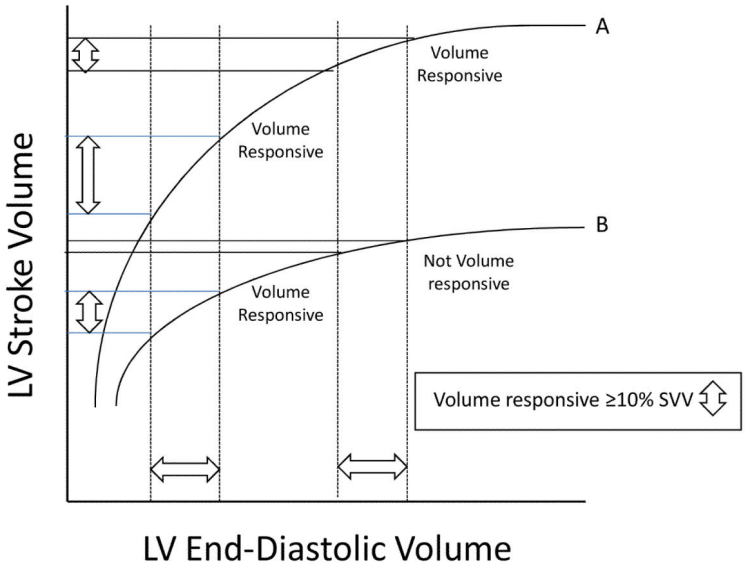

Figure 2.

Stylized display of two different Frank-Starling curves showing the relation between left ventricular (SV) stroke volume and LV end-diastolic volume. If positive pressure ventilation alters LV end-diastolic volume across a range of LV end-diastolic volumes, then LV stroke volume will also vary based on where on the Frank-Starling curve the subject is. Ay low levels of LV end-diastolic volume the LV stroke volume variability, quantified as stroke volume variation (SVV) will be greater than on the flatter portions of the curves. Thus, by assessing SVV for an appropriate degree of LV end-diastolic volume changes, one can reliably define where on the Frank-Starling relationship the patient is predicting subsequent LV stroke volume change sin response to increases in LV end-diastolic volume

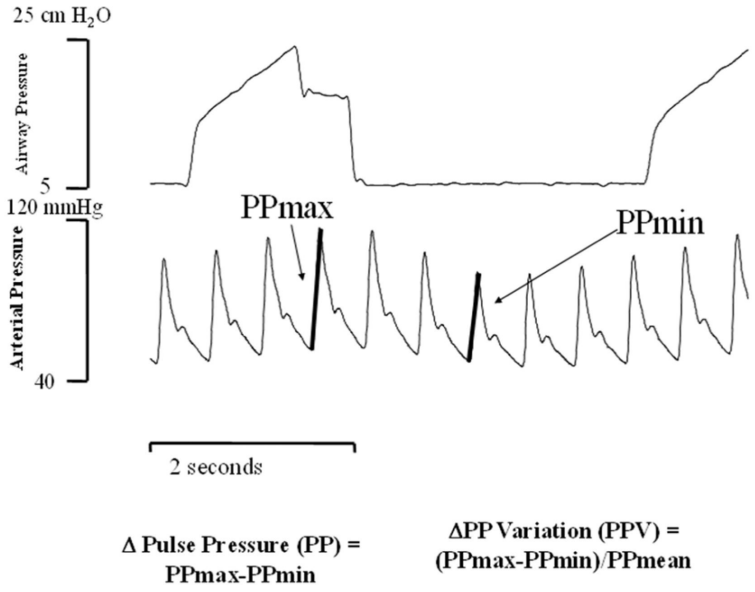

Figure 3.

A strip chart recording of airway pressure and arterial pressure over time. The ratio of the difference between the maximal (Δ) arterial pulse pressure (diastole to systole)(PPmax) and the minimal arterial pulse pressure (PPmin) to the mean pulse pressure (PPmean) defines pulse pressure variation (PPV).

Table 1

Tissue Oximetry (StO_2) in conjunction with a Vascular Occlusive Test (VOT) Predicts Death and the need for Life-Saving Interventions (LSI)

	All Patients	**LSI**	**No LSI**	
Variable	**n=194**	**n=61**	**n=133**	**p**
Pre-hospital Physiology				
Highest heart rate, bpm	98±19	100 ±19	97±19	0.34
Lowest systolic blood pressure	120±13	119±17	121±10	0.94
Highest respiratory rate, cpm	17±2	18±3	17±2	0.25
Glasgow Coma Score <15, n(%)	52 (27)	25 (41)	27 (20)	0.003
StO_2 Parameters				
Deoxygenation slope, %/sec	0.15 (0.1-0.2)	0.13 (0.1-0.17)	0.17 (0.11-0.21)	0.007
Reoxygenation slope, %/sec	2.1 (1.1-3.5)	1.9 (0.9-2.8)	2.3 (0.9-2.8)	0.13
Baseline, %	80 (74-86)	80 (74-84)	80 (86-74)	0.9
Pre-hospital serum lactate, mmol/L	2 (1.2-2.9)	2.2 (3.1-1.4)	1.8 (1.2-2.6)	0.02
	All Patients	**In-hospital Death**	**Alive at Discharge**	
Variable	**n=194**	**n=6**	**n=188**	**p**
Pre-hospital Physiology				
Highest heart rate, bpm	98±19	94±15	98±19	0.7
Lowest systolic blood pressure	120±13	123±28	120±12	0.3
Highest respiratory rate, cpm	17±2	17±2	17±2	0.9
Glasgow Coma Score <15, n(%)	53 (27)	4(67)	49(26)	0.03
StO_2 Parameters				
Deoxygenation slope, %/sec	0.15 (0.1-0.2)	0.11 (0.07-0.16)	0.15 (0.11-0.2)	0.2
Reoxygenation slope, %/sec	2.1 (1.1-3.5)	0.86 (0.7-0.9)	2.2 (1.3-3.5)	0.005
Baseline, %	80 (74-86)	77 (68-82)	80 (74-86)	0.3
Pre-hospital serum lactate, mmol/L	2 (1.2-2.9)	3.3 (2.4-3.8)	2 (1.2-2.9)	0.08

Table 2

Causes for inaccurate interpretation of PPV and SVV threshold values to define volume responsiveness

1. PPV or SVV false positives (PPV >15% or SVV >10%) but not volume responsive	
Condition	**Etiology of error**
Spontaneous ventilation	Ventricular interdependence
Acute cor pulmonale	Ventricular interdependence
Atrial fibrillation	Variable LV filling time
2. PPV or SVV false negatives (PPV <15% or SVV <10% but volume responsive)	
Condition	**Etiology of error**
Intra-abdominal hypertension	Minimal change in the driving pressure for venous return
Small tidal volumes (<8 mL/kg)	Minimal change in the driving pressure for venous return
Bronchospasm	Minimal change in the driving pressure for venous return