Management of circulatory and respiratory failure using less invasive volumetric and functional hemodynamic monitoring.

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1 Introduction/Technological considerations

In patients instrumented with a central venous line and a thermodilution arterial catheter, the transpulmonary thermodilution technique – currently available on the “PiCCOplus” monitor (Pulsion Medical Systems, Munich, Germany) and on the “CCO” cardiac output module of Philips Medical Systems - allows the simultaneous assessment of valuable cardiovascular and dynamic heart-lung-interaction parameters. After injection of an ice-cold or room-tempered saline bolus central venously, a thermistor in the tip of the arterial catheter is used to measure the downstream temperature changes. The cardiac output is then calculated by the analysis of the thermodilution curve using a modified Stewart-Hamilton algorithm. The monitor also calculates the mean transit time and the exponential downslope time of the transpulmonary thermodilution curve. The product of cardiac output and mean transit time is the volume of distribution of the thermal indicator [1]. This volume of distribution, the so-called “intrathoracic thermal volume”, is made up of the intrathoracic blood volume and the extravascular lung water (fig. 1). The product of cardiac output and exponential downslope time is the “pulmonary thermal volume” [2], which is composed of the pulmonary blood volume and the extravascular lung water (fig. 1). Therefore, the volume of blood contained in the four heart chambers – called the global end-diastolic volume (GEDV) - is easily obtained as the difference between the intrathoracic thermal volume and the pulmonary thermal volume [3,4] (fig. 1). The intrathoracic blood volume has been shown to be quite consistently 25% greater than the GEDV [4]. Therefore, the intrathoracic blood volume is estimated as 1.25 x GEDV and the extravascular lung water (EVLW) as the difference between the intrathoracic thermal volume and the intrathoracic blood volume [4] (fig. 1).
Figure 1. Assessment of global end-diastolic volume (GEDV) and extravascular lung water by transpulmonary thermodilution. (CO = cardiac output, MTt = mean transit time, RA = right atrium, RV = right ventricle, PBV = pulmonary blood volume, LA = left atrium, LV = left ventricle, DST = downslope time, ITBV = intrathoracic blood volume)
2 Transpulmonary thermodilution in shock states

2.1 Discrimination between high and low flow states

Acute circulatory failure is a clinical (cold extremities, low urine output, tachycardia ± systemic hypotension) and biological (renal or hepatic dysfunction, high lactate level…) syndrome that is usually due to a low blood pressure and/or a low cardiac output, since both pressure and flow are major determinants of organ function (fig. 2). A low cardiac output can be responsible of systemic hypotension, but a low blood pressure can also result from systemic vasodilation (fig. 2). Thus, in patients with acute circulatory failure, the measurement of cardiac output is useful to discriminate between high and low flow states, and hence to identify patients who may benefit from vasopressors (high cardiac output and low blood pressure) or volume therapy and/or inotropic drugs (low cardiac output).

![Figure 2](image)

Figure 2. Usefulness of transpulmonary thermodilution derived parameters to understand the pathophysiological mechanisms of acute circulatory failure and hence to choose the more appropriate therapeutic card (AP = arterial pressure, CO = cardiac output, SVR = systemic vascular resistance, GEDV = global end-diastolic volume, PPV = pulse pressure variation, SVV = stroke volume variation, GEF = global ejection fraction)

The measurement of cardiac output by transpulmonary thermodilution has been validated by many clinical studies as compared to pulmonary artery thermodilution [5-8] and the Fick method [9-11] both in children [8,9,11] and adult patients [5-7,10]. The reproducibility of cardiac output measured by this method is around 5% [5]. However, the measurement of cardiac output alone is generally insufficient to determine the correct therapeutic approach. In this regard, the major determinants of cardiac output, namely preload, contractility and afterload, have to be measured for gaining more insight into the pathophysiology of the circulatory failure.
### 2.2 Assessment of cardiac preload

In low flow states, assessment of cardiac preload may be useful to identify patients who may benefit from volume loading. Cardiac filling pressures (central venous, right atrial and wedge pressures), though still being widely used, are not accurate indicators of cardiac preload because of erroneous readings of pressure tracings [12], discrepancies between measured and transmural pressures (particularly in patients ventilated with high levels of PEEP or with dynamic hyperinflation) [13], and simply because the physiological relationship between ventricular end-diastolic pressure and volume depends on ventricular compliance [14]. Therefore, several volumetric (as opposed to pressure) parameters have been proposed to assess cardiac preload at the bedside (fig. 3). These include the right ventricular end-diastolic volume evaluated by fast response pulmonary artery catheters [15-17], the left ventricular end-diastolic area measured by echocardiography [18-21], the intrathoracic blood volume evaluated by the double indicator (thermo-dye) dilution technique [22-25], and more recently the GEDV that is evaluated by the easy to apply single-indicator transpulmonary thermodilution [3,4,26-28] (fig. 3). The GEDV has been shown to behave as a true indicator of cardiac preload. It increases with fluid loading but not with dobutamine, and its increase following fluid loading is correlated with the increase in stroke volume (consistent with the physiological relationship between preload and stroke volume) [26-28].

![Figure 3](image_url)

**Figure 3.** Volumetric indicators of cardiac preload available at the bedside (RV = right ventricular, LV = left ventricular).

Furthermore, although cardiac output and GEDV are derived from the same thermodilution curve, a mathematical coupling between these two parameters has been ruled out by several studies [28-30]. The assessment of GEDV does not require a pulmonary artery catheter, is possible in neonates and infants [31] (in contrast to the measurement of right ventricular end-diastolic volume), and can be repeated as often as necessary (a single cold bolus, that can be done by a nurse, is sufficient) without being operator-
dependent (in contrast to the echocardiographic measurement of left ventricular end-diastolic area).

2.3 Prediction of fluid responsiveness

The real clinical endpoint of fluid loading in low flow states, is not to “normalize” but to adjust preload with regard to the underlying pathology in order to achieve an increase in cardiac output using the volume pathway. Therefore, predictors of fluid responsiveness (i.e. of a significant increase in cardiac output in response to volume) are needed at the bedside. Because the slope of the relationship between ventricular preload and stroke volume depends on ventricular contractility, assessing ventricular preload alone is not sufficient to predict fluid responsiveness [32]. Even volumetric indicators of cardiac preload have been shown to be useful in predicting volume expansion efficacy only when they are low or high, but not for intermediate values [32]. In this regard, dynamic parameters, mainly the changes in left ventricular stroke volume during mechanical ventilation, have been shown to predict the hemodynamic effects of fluid loading [33,34]. In deeply sedated mechanically ventilated patients, the respiratory changes in left ventricular stroke volume reflect the sensitivity of the heart to changes in preload induced by mechanical insufflation, and hence the sensitivity of the heart to a potential volume loading [34]. The response of the left ventricular stroke output to a mechanical breath can be estimated by the systolic pressure variation and its dDown component [20,35]. However, because the arterial pulse pressure (systolic minus diastolic pressure) is directly proportional to left ventricular stroke volume, the respiratory changes in pulse pressure have been shown to reflect even more closely those of left ventricular stroke volume, and hence to accurately predict fluid responsiveness [36] (fig. 4). The pulse pressure variation (PPV), defined as the percentage of variation of arterial pulse pressure over a floating period of 7.5 seconds, a parameter very close to the respiratory changes in pulse pressure, is now automatically calculated and displayed on the PiCCOplus monitor.

Figure 4 The respiratory changes in arterial pulse pressure accurately predict fluid responsiveness (adapted from [36])
In addition, the PiCCOplus monitor also directly measures the left ventricular stroke volume by pulse contour analysis of arterial pressure. The algorithm used analyses the shape and the area under each stroke and uses mean stroke volume derived from transpulmonary thermodilution cardiac output to calculate the actual patient specific arterial compliance and impedance. Then compliance, impedance and the incremental changes of arterial pressure wave form yield continuous pulse contour stroke volume and cardiac output. Thus, the PiCCOplus monitor is able to provide a beat-to-beat measurement of stroke volume in real time, including the continuous calculation of the stroke volume variation (SVV). The SVV is defined as the percentage change in stroke volume over a floating period of 7.5 seconds. The continuously measured pulse contour cardiac output has been shown to be accurate in many studies [7,37-42]. Like changes in pulse pressure, the SVV has been shown to be an accurate predictor of fluid responsiveness in patients undergoing brain [43] and cardiac surgery [44,45].

2.4 Assessment of cardiac contractility/function

In low flow states, assessment of cardiac contractility/function can be useful to identify patients who may benefit from the administration of inotropic agents. Accurate bedside assessment of cardiac contractility is very difficult since all hemodynamic parameters are more or less dependent on afterload and preload conditions [46]. Nevertheless, the ventricular ejection fraction, which is the ratio of stroke volume to ventricular end-diastolic volume, is commonly used to assess ventricular function [46] (fig. 5). Since the transpulmonary thermodilution provides the GEDV, which is the volume of blood contained in the four heart chambers, the ratio of stroke volume to a quarter of the GEDV represents the global ejection fraction (GEF) of the heart. This parameter, automatically calculated and displayed by the monitor, can be used to identify patients with right or/and left ventricular dysfunction (fig. 5).
Figure 5. Bedside available indicators of cardiac function (RV = right ventricular, RVEDV = RV end-diastolic volume, SV = stroke volume, LV = left ventricular, LVEDV = LV end-diastolic volume, GEDV = global end-diastolic volume).

3 Transpulmonary thermodilution in hypoxemic patients

3.1 Detection of patients with pulmonary edema

Chest X-ray, arterial blood gases and hence the current international definition of ALI/ARDS have been shown to be of little value in identifying patients with pulmonary edema [47-51]. Several techniques have been proposed to assess EVLW in humans [52-54]. Among these techniques, double indicator (thermo-dye) dilution has been used most frequently in ICU patients [55-61], since other techniques (CT scan, nuclear magnetic resonance imaging, positron emission tomography) are not available at the bedside. The double indicator dilution technique is, however, relatively time consuming, cumbersome and expensive, and therefore has not been widely incorporated into clinical practice. The assessment of EVLW by a single (cold) indicator has been recently validated against the double indicator (thermo-dye) dilution technique [3,4] and the reference gravimetric method [62]. Therefore, the transpulmonary thermodilution technique allows the reliable bedside assessment of EVLW in critically ill patients using a simple cold saline bolus. Since the maintenance of negative fluid balance has been shown to improve the outcome of patients with pulmonary edema [57], the assessment of EVLW is useful to identify and follow patients who may benefit from such a therapeutic strategy. In other words, the routine measurement of EVLW may settle the ongoing controversy between the “dry” and “wet” therapeutic approach of patients with ARDS [63]. Clinical studies are urgently needed to confirm this significant potential value of EVLW measurements. Finally, since the beneficial effects of fluid restriction/depletion in patients with pulmonary edema may be associated with worsening hemodynamics, the simultaneous assessment of cardiac preload (GEDV) and of the sensitivity of the heart to changes in preload (PPV and SVV) can be very helpful to deal with this issue.

3.2 Assessment of pulmonary vascular permeability

By definition, EVLW is increased in both permeability and hydrostatic pulmonary edema. In hydrostatic pulmonary edema, the increase in EVLW is due to an increase in pulmonary blood volume and pressure. Therefore, the ratio of EVLW to pulmonary blood volume is much higher in case of permeability than in case of hydrostatic pulmonary edema (fig. 6). The pulmonary blood volume is easily estimated by the PiCCOplus monitor as 25% of the GEDV [4]. Therefore, the ratio of EVLW to pulmonary blood volume – called the pulmonary vascular permeability index (PVPI) [60] - is automatically calculated and displayed by the PiCCOplus monitor. This parameter may be useful not only to discriminate between hydrostatic and permeability edema but also to assess the effects of various disease states and therapeutic interventions on pulmonary vascular permeability [60].
The pulmonary vascular permeability index (PVPI) is calculated as the ratio of extravascular lung water (EVLW) to pulmonary blood volume (PBV). The PVPI is greater in permeability than in hydrostatic pulmonary edema.

3.3 Mechanisms of arterial hypoxemia

The main mechanisms of arterial hypoxemia are ventilation/perfusion mismatch and intrapulmonary shunt. However, other mechanisms – mainly the “PvO2 effect” and a right-to-left intracardiac shunt - may also contribute to arterial hypoxemia.
• "PvO$_2$ effect"

In patients with increased intrapulmonary shunt, PvO$_2$ is a major determinant of PaO$_2$ [64]. By increasing peripheral oxygen extraction and hence decreasing PvO$_2$, a decrease in cardiac output is able to worsen arterial hypoxemia. In this context, increasing cardiac output either by fluid loading or by inotropic agents may result in increased PvO$_2$, which in turn may improve PaO$_2$ [64]. Therefore, the measurement of cardiac output is important to rule out a low cardiac output and a possible "PvO$_2$ effect" in the presence of arterial hypoxemia. Moreover, the assessment of cardiac preload (GEDV) and of dynamic markers of fluid responsiveness (PPV and SVV) is useful to choose the most appropriate therapy to improve cardiac output.

• Right-to-left intracardiac shunt

Intracardiac shunt from the right to the left atrium through a patent foramen ovale may also cause hypoxemia. A patent foramen ovale is present at autopsy in 20 to 34% of the general population [65]. The unique nature of this membranous structure allows it to function as a unidirectional valve, opening from right-to-left. The prevalence of right-to-left intracardiac shunt is around 25% in patients with pulmonary hypertension [66] or during positive pressure ventilation [67] and is potentiated by positive end-expiratory pressure (PEEP) [68]. In patients with ALI/ARDS, the real prevalence of RL intracardiac shunt is unknown and may be clinically significant because of the usually associated pulmonary hypertension, mechanical ventilation, and PEEP. Color Doppler examination of interatrial septum and contrast echocardiography can diagnose right-to-left intracardiac shunt [67,68] but are not routinely performed in ALI/ARDS patients. A right-to-left intracardiac shunt is easily (a single cold saline bolus…) evidenced by the visual inspection of the transpulmonary indicator dilution curve [69] (fig. 7). Indeed, in case of right-to-left intracardiac shunting, one part of the indicator passes through the interatrial septum and reaches rapidly the thermistor-tipped arterial catheter. As a result, the transpulmonary dilution curve appears prematurely and becomes biphasic [69] (fig. 7). Early recognition of such a shunt may have therapeutic implications such as nitric oxide inhalation [70] or PEEP decrease/removal [68]. The efficacy of these maneuvers can be immediately checked by the mere observation of the shape of the transpulmonary indicator dilution curve.
3.4 Prediction of PEEP-induced hemodynamic instability

In ventilated patients with ALI/ARDS, PEEP may improve pulmonary gas exchange. However, it may also decrease cardiac output and thus offset the expected benefits in terms of oxygen delivery. The PEEP-induced decrease in cardiac output is assumed to be mainly due to a decrease in systemic venous return secondary to the increased pleural pressure [71,72]. The adverse hemodynamic effects of PEEP are not predicted by conventional static hemodynamic parameters. In contrast, the respiratory changes in left ventricular stroke volume – assessed by arterial waveform analysis - have been shown to be closely related to the decrease in cardiac output in response to PEEP application [73,74], such that the higher the respiratory changes in arterial pressure on ZEEP, the more marked the decrease in cardiac output after PEEP application [74]. Therefore, PPV and SVV can also be used to predict and hence to prevent the deleterious hemodynamic effects of PEEP.

4 Overview

Most of the hemodynamically unstable and/or severely hypoxemic patients are instrumented with a central venous line and an arterial line. Thus, advanced cardio-respiratory monitoring by the transpulmonary thermodilution method simply requires the use of a specific thermodilution arterial catheter, without any further invasive and costly instrumentation. In patients with circulatory failure, the transpulmonary thermodilution technique allows the simultaneous assessment of cardiac output, cardiac preload (GEDV), cardiac contractility/function (GEF) and the prediction of fluid responsiveness (PPV and SVV). Therefore, the transpulmonary thermodilution allows a better understanding of the pathophysiological mechanisms
(vasoplegia, hypovolemia, heart failure) of acute circulatory failure and hence the choice of the most appropriate therapy (fig. 2). In contrast to echocardiography, transpulmonary thermodilution is a non-operator dependent technique that can be used by all caregivers, in all ICUs, as often as is necessary, and that provides all hemodynamic parameters within few minutes. In hypoxemic patients, transpulmonary thermodilution enables the identification of patients with pulmonary edema (elevated EVLW) as well as the quantification of pulmonary edema and its response to therapeutic maneuvers (e.g. fluid restriction/depletion). In addition, it enables the assessment of pulmonary vascular permeability (PVPI), a better understanding of the pathophysiological mechanisms of hypoxemia (pulmonary edema, low cardiac output, right-to-left intracardiac shunt), and the prediction of the possible deleterious hemodynamic effects of PEEP. In conclusion, the transpulmonary thermodilution technique provides the caregiver a simple, reproducible and integrated approach of the heart and the lungs (cardio-respiratory monitoring) that cannot be considered separately in most critically ill patients.

References
