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REVIEW

Alternatives to the Swan–Ganz catheter

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Abstract

While the pulmonary artery catheter (PAC) is still interesting in specific situations, there are many alternatives. A group of experts from different backgrounds discusses their respective interests and limitations of the various techniques and related measured variables. The goal of this review is to highlight the conditions in which the alternative devices will suffice and when they will not or when these alternative techniques can provide information not available with PAC. The panel concluded that it is useful to combine different techniques instead of relying on a single one and to adapt the "package" of interventions to the condition of the patient. As a first step, the clinical and biologic signs should be used to identify patients with impaired tissue perfusion. Whenever available, echocardiography should be performed as it provides a rapid and comprehensive hemodynamic evaluation. If the patient responds rapidly to therapy, either no additional monitoring or pulse wave analysis (allowing continuous monitoring in case potential degradation is anticipated) can be applied. If the patient does not rapidly respond to therapy or complex hemodynamic alterations are observed, pulse wave analysis coupled with TPTD is suggested.

Keywords: Hemodynamic monitoring, Cardiac output, Tissue perfusion, Cardiac failure

Introduction

Human right heart catheterization was first performed in 1929 by Werner Forssmann and then developed by André Cournand and Dickinson W. Richards, the three authors receiving the Nobel Prize for it in 1956 [1]. It was in the 1970s, when Drs. Swan and Ganz added balloon flotation [2] and thermodilution [3] to the catheterization technique, that the pulmonary artery catheter (PAC) became popular. The PAC has been considered useful, useless, and even harmful [4–6]. A meta-analysis of PAC efficacy and safety in 5051 patients (13 RCTs) showed no evidence of harm or of a conferred overall benefit [7]. These studies mostly demonstrated that PAC is safe when properly used. Recent studies have suggested better outcomes in selected patients with heart failure and trauma when a PAC was part of a given strategy of care [8, 9]. Still, no monitoring device will improve patient outcomes unless coupled to a treatment that itself improves outcomes [10, 11].

As the PAC is a multifaceted hemodynamic monitor, its use is complex. When using all its capabilities, it offers measurement of pulmonary artery pressure, pulmonary artery occlusion pressure (PAOP), right atrial pressure (RAP), cardiac output (CO), and mixed-venous oxygen saturation (SvO_2). Pulmonary artery capillary pressure can be estimated and up to ten additional variables can be calculated [12]. Using all of this at the bedside is a challenge to even the most experienced clinician. However, the unique data available from a PAC make it an attractive hemodynamic monitor in the care of patients with severe circulatory shock, particularly those with right ventricular (RV) dysfunction and/or acute respiratory failure, as recommended by the ESICM task force [13].

Due to concerns about the invasiveness of the PAC, less or even non-invasive techniques have become available [14]. Alternative techniques, including minimally

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invasive monitoring and echocardiography, can display many of the hemodynamic values and variables captured by the PAC. Some of these devices can offer information in addition to that available with a PAC.

It is important to know the intrinsic value and limitations of variables measured by the alternative devices, as well as the missing information, and to determine in which conditions these devices will or will not suffice or when these alternative techniques can provide information not available with the PAC (Table 1). This ambitious review/consensus article aims to address many of the issues involved in the use of these alternative hemodynamic monitoring devices.

Clinical indices of tissue perfusion

In the early phase of circulatory shock, clinical examination offers valuable information. Tachycardia, delirium/confusion, anxious breathing, cold and clammy skin, and persistent purpura are among the prominent

Table 1 Comparisons of variables obtained by the pulmonary artery catheter and alternative methods

Variables measured by PAC	Alternatives to PAC	Comments
Cardiac output measurements by thermodilution	Pulse wave, non-calibrated (PWNC)	PAC measurements intermittent or semi-continuous PWNC continuous measurements (beat by beat); less precise and accurate but satisfactory for trends
	Pulse wave, calibrated (PWC)	PWC continuous measurements (beat by beat); precise and accurate but require recalibration
	Transpulmonary and lithium thermodilution	(virtually) As reliable as the PAC thermodilution
	Echocardiography	Reliable provided measurements performed in the left ventricular outflow tract
	Esopageal Doppler	Estimates cardiac output from lower body flow; relevance of aortic diameter assessment
	Bioimpedance/bioreactance	Precision and accuracy challenged in severe conditions but satisfactory for trends
PAOP	Volumes and extravascular lung water by TPTD	Relationship between volumes and pressure is curvilinear PAOP by PAC affected by pleural-pericardial-abdominal pressure Volumetric indices do not differentiate right and left side
	Echocardiography	Semi-quantitative measurement (low-average-elevated) and for trends
	Dynamic indices of fluid responsiveness	Accurate assessment of the response to fluids but do not evaluate increase LAP
RAP	CVP	Almost identical if central catheter correctly positioned
	Echocardiography	Only as a semi-quantitative measurement (low-average-elevated)
Pulmonary artery pressure (PAP)	Echocardiography	Echo provides reliable measurements of PAP provided CVP is invasively measured
SvO2	ScvO2	Not identical (as lower body not taken into account in ScvO2) but satisfactory agreement for bedside use
PvaCO2	PvaCO2 with PvCO2 via a central line	Not identical (as lower body not taken into account in ScvO2) but satisfactory agreement for bedside use
Variables not measured by PAC		
	Clinical indices of tissue perfusion	Do not identify the cause of the hypoperfusion The area investigated may not reflect other areas
	Microcirculation	The area investigated may not reflect other areas
	Lactate	Not always of hypoxic origin Slow changes in lactate concentrations

PAC pulmonary artery catheter, *TPTD* transpulmonary thermodilution, *PAOP* pulmonary artery occluded pressure, *RAP* right atrial pressure, *CVP* central venous pressure, SvO_2 mixed-venous oxygen saturation, $ScvO_2$ central venous oxygen saturation, $PvaCO_2$ veno-arterial difference in PCO_2

abnormalities and are used to characterize patients with shock and assess tissue perfusion [15].

Relatively simple subjective measures of peripheral perfusion exist in addition to more objective measures [16]. The subjective assessment of the skin temperature, temperature of the great toe, temperature difference between the great toe and central temperature/ambient temperature, and skin temperature difference between the distal arm and finger all have clinical relevance [17–19]. The major issues are to determine whether the reference should be ambient or central temperature and to which extent therapy should be influenced by temperature differences.

Measurements of skin perfusion using optical techniques also relate to outcome in critically ill patients. The perfusion index (PI) derived from the pulse oximetry signal and tissue hemoglobin saturation (StO_2) measured by near infrared spectroscopy are related to the progression of organ failure, failure to decrease lactate levels, and increased morbidity and mortality [19–22]. However, both methods are influenced by decreased skin temperature [20, 22]. Nevertheless, these devices provide continuous monitoring, which is a real advantage.

Assessments of skin mottling and capillary refill time are two methods that stand out because of their immediate availability at no cost without requiring specific equipment. Mottling has been shown to be a strong predictor of early mortality in septic shock patients [23, 24]. Scoring of mottling allows for better quantification of the response to therapy. In addition, the discolored skin areas relate to decreased StO_2 [25] and prolonged capillary refill time [26]. The latter has also been shown to be related to increased morbidity and mortality and decreased visceral organ perfusion in critically ill patients [26, 27].

There are important limitations to these indices. First, while both identify issues with peripheral perfusion, the nature of the cause of tissue hypoperfusion (septic vs. low-output shock) remains to be identified by other hemodynamic monitoring devices. Second, peripheral perfusion may fail to reflect more central tissue perfusion [28] and may be affected by local arteriopathy.

Finally, are these indices simple disease identifiers (trigger for therapy) or can they be used as a target of therapy (should we aim at improving them and, if yes, to what goal)? Indicators of abnormal peripheral perfusion can be improved by a titrated infusion of nitroglycerin [29]. In septic shock patients, targeting fluid resuscitation based on peripheral perfusion may be safe and associated with less fluid administration compared with therapy based on systemic hemodynamic variables [18].

Biologic indices of tissue perfusion

The measurement of central venous oxygen saturation ($ScvO_2$) is often taken as a surrogate of SvO_2, but it is not equivalent to it. $ScvO_2$ is measured in blood drained from the upper part of the body but not blood drained from the lower part and coronary sinus. As splanchnic organs represent one-fourth to one-third of the cardiac output and as preferential desaturation occurs in the splanchnic area in shock states [30], O_2 saturation in hepatic veins can markedly affect the agreement between SvO_2 and $ScvO_2$. In normal conditions, the SvO_2 value is slightly higher than that of $ScvO_2$ because of the contribution of the very high renal venous O_2 saturation. In shock states, the SvO_2 value is usually lower than that of $ScvO_2$ because of the more significant decrease in venous saturation in the splanchnic and renal circulation. Hence, even though globally correlated [31], $ScvO_2$ is less sensitive to decreased perfusion compared with SvO_2. $ScvO_2$ gives no indication of the origin of the hemodynamic alteration. In addition, it is frequently elevated in distributive shock because of microcirculatory alterations and/or cellular dysfunction. Despite these limitations, it is important to measure $ScvO_2$ to help in the interpretation of the data gathered by the other hemodynamic devices. In sum, a low $ScvO_2$ value reflects circulatory stress, whereas a normal $ScvO_2$ value does not ensure circulatory sufficiency.

Blood lactate is a key marker of tissue hypoperfusion. In experimental conditions, there is a sharp rise in lactate once oxygen consumption becomes limited by oxygen transport, a condition that defines shock [13]. As such, it is one of the key measurements to obtain in the management of shock [15, 32]. There are nevertheless two potential issues in the interpretation of lactate measurements. First, lactate is not only of hypoxic origin, but can also result from the activation of glycolytic pathways under the influence of inflammation or catecholamines [33]. Second, while lactate levels rise sharply in case of hypoxia, the decrease in lactate values may take time as its clearance may also be affected. Nevertheless, looking at lactate levels and their kinetics is recommended in the management of shock states [32].

Measurements of the gradient between venous and arterial PCO_2 ($PvaCO_2$) can also be informative in the evaluation of the adequacy of tissue perfusion. In normal conditions, this gradient is ≤ 6 mmHg, so that a gradient > 6 mmHg suggests an inadequate tissue perfusion. Increased $PvaCO_2$ may be the consequence of inadequate cardiac output (then $ScvO_2$ levels should also be low) or microcirculatory dysfunction (then $ScvO_2$ levels would usually be high) [34, 35].

It is important to realize that $ScvO_2$, lactate and $PvaCO_2$ values indicate that there is a circulatory problem, but none of these indicate the origin of the problem. Combination of these biologic measures with other hemodynamic variables is hence recommended [14].

Central venous pressure: uses and misuses

The central venous pressure (CVP) is measured at the tip of a central venous catheter. Its normal value ranges between 0 and 3 mmHg. It is an accepted surrogate of RAP.

CVP can be used for several purposes:

- To optimize tissue perfusion pressure: As CVP is the back pressure for venous return, an elevated CVP results in an elevated tissue capillary pressure—causing "hydrostatic" tissue edema—and may compromise organ perfusion by decreasing organ perfusion pressure. In practice, to select the optimal mean arterial pressure (i.e., the upstream pressure for organ blood flow), CVP should be taken into account when it is high and neglected when it is low.
- To guide fluid resuscitation: CVP is also considered representative of the RV filling pressure and hence an estimate of RV preload. However, both assumptions may not be correct in all conditions. First, CVP represents the RV filling pressure only if the RV surrounding pressure is neither too elevated nor too low. The RV surrounding pressure is either pericardial or intrathoracic pressure, whichever is higher [36]. To minimize increased intrathoracic pressure effects, CVP must be measured at end-expiration. However, in cases of (extrinsic or intrinsic) positive end-expiratory pressure, the measured CVP overestimates the transmural CVP. Transmural CVP is difficult to determine in practice. Second, the relationship of RV filling pressure and RV preload is complex: Under normal conditions, the RV distending pressure increases little during filling as the RV dilates. In cases of RV overdistension or hypertrophy, the opposite phenomenon occurs so that increases in CVP overestimate increases in RV volume. Consequently, CVP and its changes are not markers of RV preload. Importantly, even if we assume CVP to reflect RV preload, it is a rather poor marker of preload responsiveness. Indeed, due to inter-individual differences in the RV preload-stroke volume relationships (Frank-Starling mechanism), assessing preload is not assessing preload responsiveness. Therefore, a marker of preload cannot reliably predict fluid responsiveness, even though extreme values can be useful to predict the response to fluids [37]. Hence, recent guidelines suggest the use of dynamic markers of fluid responsiveness for fluid resuscitation in septic patients [13, 32]. Nevertheless, dynamic evaluation of CVP can be used to evaluate the patient's tolerance of fluid administration [37].
- To evaluate right ventricular dysfunction: As reported above, the relationship between the CVP and right ventricular volume is curvilinear. Hence, a significant right ventricular dysfunction is associated with an increased CVP.

In summary, CVP is important: (1) to estimate the backpressure for venous return and (2) to identify situations of high RV filling pressures (transmural CVP should be considered) and hence of RV dysfunction (to be confirmed by echocardiography). The CVP is a poor predictor of fluid responsiveness, but a dynamic evaluation of CVP can be used to assess the patient's tolerance to fluid.

Cardiac output measurement by pulse wave analysis

The estimation of stroke volume (SV) and CO based on the mathematical analysis of the arterial blood pressure waveform is called pulse wave analysis, pulse pressure analysis, or pulse contour analysis. Left ventricular SV is one of the primary variables defining arterial pulse pressure, so extrapolating SV from pulse pressure seems reasonable.

Numerous algorithms have been developed to assess CO using pulse wave analysis [14, 38]. The shape of the waveform depends on various factors including ventricular ejection, aortic impedance, arterial compliance, and vasomotor tone that all influence the velocity of the pressure wave in large arteries and the degree of pressure wave reflection in peripheral arteries [14].

The arterial blood pressure waveform used for pulse wave analysis can be recorded invasively with an arterial catheter or noninvasively with probes placed on the patient's finger (vascular unloading technology, also called the volume clamp method or simply the finger cuff technology) or over the radial artery (automated radial artery applanation tonometry). The measurement performance of pulse wave analysis depends on the impeccable quality of the arterial blood pressure waveform, which is often impaired in severely vasoconstricted patients.

Depending on the system used, the pulse wave analysis-derived values of SV or CO can be "uncalibrated" or "calibrated" to external values (e.g., obtained with dilution techniques). Calibration of the CO value to an external reference CO value increases the accuracy and precision of pulse wave analysis-derived CO measurements and is recommended in patients with deceased vasomotor tone such as septic patients or patients with liver failure [14]. However, these require frequent re-calibration, especially

when vascular tone changes [39]. Uncalibrated systems estimate values of CO solely by analyzing the characteristics of the arterial pressure waveform and using patient-specific anthropometric, biometric, and demographic data. Uncalibrated systems differ in the way they assess the extent to which changes in the shape of the arterial pressure waveform are caused by changes in SV and/or changes in vascular tone. In most cases, the accuracy and precision of uncalibrated devices are moderate to poor [40, 41], but changes induced by fluids can reliably be tracked. Some systems use dedicated algorithms to also take into account vascular tone. While initial versions were not reliable in patients with low vascular tone [42], recent developments have made these more reliable even in these patients [43, 44].

Whatever the system used, marked and/or rapid changes in peripheral vascular resistance may affect the reliability of CO measurement from pulse wave analysis [39, 45]. In calibrated methods, recalibration helps to regain accuracy [39]. Uncalibrated methods assessing vascular tone require time to recover accuracy, and reliability is lost until the new equilibrium is reached.

The main advantage of pulse wave analysis is that it provides a continuous estimation of real-time CO allowing immediate detection of changes in CO in response to time, treatment, or maneuvers. As the value of SV may change with each single beat, pulse wave analysis also provides dynamic cardiac preload variables [respiratory variations in pulse pressure (PPV) and SV or response in cardiac output during a passive leg-raising test]. These indices outperform filling pressures in the prediction of fluid responsiveness and are now recommended for the management of shock and sepsis [13, 32].

The main disadvantage of most methods (except devices calibrated by transpulmonary thermodilution—see below) is that minimal information is provided beyond cardiac output measurements and dynamic cardiac preload variables, making their use less relevant in complex patients.

Transpulmonary thermodilution

Transpulmonary thermodilution (TPTD) is used to calibrate some pulse contour/pulse wave analysis devices. Transpulmonary thermodilution is as reliable as right-sided thermodilution for the measurement of CO.

In addition to CO, TPTD provides the following variables: the global end-diastolic volume (GEDV), which assesses preload volumetrically; the extravascular lung water (EVLW), which assesses the degree of pulmonary edema [46]; and the pulmonary vascular permeability index (PVPI), which may help to differentiate between cardiogenic and permeability pulmonary edema [47]. The respective advantages and disadvantages of the different variables are presented in Table 2. Of note, EVLW and PAOP do not provide identical information. EVLW provides information on the amount of fluid accumulated in the lung, while PAOP (or, even better, true pulmonary artery capillary pressure, which unfortunately is difficult to measure in routine practice) represents the instantaneous hydrostatic driving force.

As filling pressures with PAC, measurement of cardiac volumes is mostly interesting for the evaluation of cardiac function. Like any other static measurement, cardiac volumes do not predict the response to fluids. In addition, it is impossible to differentiate between right- and left-side dilation when faced with an increased end-diastolic

Table 2 Advantages and drawbacks of transpulmonary thermodilution devices

	Advantages	Drawbacks
Measurement of cardiac output	Continuous, real-time measurement with calibrated pulse contour analysis, intermittent but accurate with TPTD	Pulse contour analysis needs to be regularly recalibrated
Estimation of cardiac preload by cardiac volumes	Volumetric measurement of cardiac preload might be superior to filling pressures in selected conditions	Preload may not reflect preload responsiveness Volumes may not reflect left ventricular end-diastolic pressure No difference between right-left side volumes
Assessment of fluid responsiveness	Measurement of PPV and SVV Beat-by beat measurement of stroke volume allows the performance of tests such PLR and ROT	Prerequisites and limitations of the different tests
Assessment of pulmonary edema	Direct estimation through extravascular lung water and pulmonary vascular permeability index	Not always feasible to dissociate ARDS from hydrostatic lung edema
Detection of cardiac dysfunction	Detection through the global ejection fraction or cardiac function index	No distinction between right and left ventricular function

PLR passive leg raising, *PPV* pulse pressure variation, *ROT* respiratory occlusion tests, *SVV* stroke volume variation, *TPTD* transpulmonary thermodilution, *ARDS* adult respiratory distress syndrome

volume. Hence, echocardiography is required to confirm the diagnosis when alterations in cardiac volumes are noticed.

Interestingly, a recent trial looking at the interpretation of simultaneously obtained TPTD and critical care echocardiography data in 127 patients with septic shock found good agreement with the concordance of therapeutic decisions in 78% of the patients [48]. While this does not imply that similar findings would be observed in other types of shock, this illustrates the clinical interest of the measured variables.

The combination of all the measured variables makes TPTD a valuable, less-invasive alternative to the PAC, especially in complex situations, such as hemodynamic instability associated with acute respiratory distress syndrome (ARDS), when each of the possible interventions may carry significant harm ('therapeutic conflict'). In particular, fluid management based on fluid responsiveness variables has a better rationale than those based on filling pressures. The simultaneously measured EVLW and PVPI may identify patients at risk of pulmonary edema during fluid administration.

The additional information provided by TPTD has been shown to significantly alter physicians' therapeutic decisions [49]. Together with the PAC, the use of TPTD has been recommended in the management of patients in severe shock and complex situations [13, 14]. While volumetric indices and intravascular pressures are physiologically related, the information on cardiovascular function provided by TPTD and PAC may sometimes diverge because of the curvilinear aspect of pressure/volume curves and errors in measurements. In most cases, the two techniques result in similar diagnostic classification [50], but divergence can be observed in some patients [50, 51].

Although considered to be less invasive than the PAC, TPTD still necessitates the insertion of a central venous catheter and the cannulation of a large artery (usually the femoral artery). The most commonly reported complications were small local hematomas (4.5%) and infections (2%) [52].

Direct head-to-head comparisons of outcomes with the two techniques are very limited. In a cohort of patients monitored with either TPTD or PAC, patients with TPTD had a greater positive fluid balance and fewer ventilator-free days compared with those with PAC [53]. There was no difference after adjustment for potential confounding factors. In a small randomized trial, no difference in survival was observed; nevertheless, the duration of mechanical ventilation was shorter with the PAC in the subgroup of patients with impaired cardiac function but not in the patients with ARDS [54].

In summary, compared with the PAC, TPTD provides an equally accurate CO, better assessment of fluid status, and the unique measurement of the EVLW, which can be helpful in cases of ARDS. Its main disadvantage is its poor ability to distinguish between right and left ventricular performance.

The role of echocardiography and lung ultrasounds

Echocardiography is being increasingly used in critically ill patients [55]. It is nowadays more frequently used than the PAC in patients with sepsis or congestive heart failure [55]. Echocardiography is usually considered an alternative to PAC for measuring and monitoring CO, but this is questionable. While the PAC may give continuous access to CO, echocardiography only provides an intermittent measurement. A recent systematic review of the literature reported that PAC and echocardiography were not interchangeable for evaluating CO and that, from an evidence-based point of view, echo studies were methodologically limited [56]. However, the disagreement mostly came when old studies were included, and new studies with better methodology for determining CO found better agreement [57]. Importantly, trends in CO, which are much more important in clinical practice than absolute CO values, are accurately detected by echocardiography [56].

For measuring CO, echocardiography has some advantages over PAC. First, echocardiography is less invasive, even with the transesophageal approach [58]. Second, echocardiography can be used in some situations in which PAC is limited, such as massive tricuspid regurgitation or very low flow states. Third, in contrast to PAC, echocardiography provides a beat-to-beat measurement of SV, which allows the assessment of fluid responsiveness through dynamic indices. Finally, and more importantly, echocardiography in the ICU provides much more information besides CO.

The concept of critical care echocardiography (CCE) nicely reflects the ubiquitous utility of echocardiography in the management of critically ill patients [59]. By its ability to directly visualize the heart function, echocardiography is unique in defining the mechanism of shock [15]. In contrast to the PAC, it provides a direct evaluation of left and RV function and of valvular structure. In patients with circulatory failure, a quick assessment of heart function by CCE is recommended, after having eliminated obvious hypovolemia [11, 13, 14]. One of the most important advantages of CCE is the understanding of heart-lung interactions in mechanically ventilated patients [60]. By assessing the right cardiac function, CCE provides important hemodynamic information to guide hemodynamic and respiratory therapy [61]. Among

all its potential applications, CCE also allows evaluating the need for fluids through several dynamic indices, which is not possible with the PAC [62]. Finally, CCE is a unique tool that detects left ventricular diastolic dysfunction, which is strongly associated with weaning failure [63] and mortality in septic shock [64].

One of the most important limitations of echocardiography is its intermittent nature. Continuous miniaturized TEE has been developed [65], but these techniques only offer limited information beyond fluid responsiveness and visual evaluation of the ventricles as quantitative Doppler assessment is not feasible. Accordingly, measurements of filling pressures, pulmonary artery pressure, and cardiac output are not feasible with these devices.

Intensivists can also use the ultrasound probe for lung ultrasonography. The latter accurately detects pulmonary edema, condensation, pneumothorax, or pleural effusion [66]. Combining these approaches of critical care ultrasonography may be useful in situations with both respiratory and circulatory failures, such as pulmonary embolism, pulmonary edema (cardiogenic or non cardiogenic), sepsis-related pneumonia, or weaning failure [67].

Evaluating the microcirculation

Microvascular abnormalities are commonly observed in critically ill patients [68–70]. These are characterized by heterogeneity in perfusion, which results in hypoxic areas coexisting with over-perfused areas. Their severity and duration are associated with organ dysfunction and mortality [69, 71, 72]. Various mechanisms may be implicated [73].

Conventional hemodynamic tools often fail to detect it. Different hand-held microscopes are used for direct observation of microcirculation, mostly applied to the sublingual area [69–71, 74, 75]. The advantage of these devices is that they are non-invasive and easy and fast to use. Exploration of the microcirculation is intermittent but can be frequently repeated without inconvenience to the patient. Importantly, evaluation of the microcirculation requires acquisition of good quality images and a strict protocol for image analysis [76, 77].

Videomicroscopes cannot be used in all circumstances. They require technical skills and patient cooperation; they are also difficult to apply in dyspneic patients. Hence, alternative ways to routinely evaluate microcirculatory alterations are desired. Clinical signs of peripheral tissue hypoperfusion may fail to detect central alterations in microvascular perfusion [28]. Blood lactate levels are often increased in patients with microvascular alterations, but the slow changes in lactate kinetics make it a very indirect marker of microvascular dysfunction. Due to local shunting, SvO_2 is not a good reflect of microvascular alterations. Interestingly, an increase in $PvaCO_2$ is a good indicator of microvascular perfusion abnormalities [34], especially when the SvO_2 value is normal, and changes in $PvaCO_2$ reflect changes in microvascular perfusion more than changes in CO [34].

An important question is whether microcirculation targeted therapy is superior to "classical" hemodynamic monitoring once satisfactory systemic hemodynamic targets have been reached. At this stage, it seems premature to address this question. While there is no doubt that a better understanding of the pathophysiologic processes is desired, the major actual limitation is that we lack therapies specifically acting at the microcirculatory level. Fluids given in the early stages [78, 79] and dobutamine [80] may somewhat improve the microcirculation, but their effects are quite variable. Vasodilatory agents may improve the microvascular perfusion, but they lack selectivity and increase flow in already perfused areas as well. Modulation of endothelial nitric oxide synthase with various agents (including vitamin C) appears promising. Hence, it is important to understand the microcirculatory changes that occur with various therapies to plan resuscitation targets for the future.

Specificities in limited resource settings

Resource-limited settings include not only parts of the developing world where lack of healthcare funds lead to limited access to medical resources, but also include areas with limited access to monitoring within the hospital in developed countries, such as the emergency department and wards. The different hemodynamic resources available in these areas are presented in Table 3.

Acute circulatory failure can be assessed using the three clinical windows for tissue perfusion [13, 15]: altered mentation, cold and mottled skin and oliguria, and with tachycardia and hypotension. The computation of the "shock index", (ratio of heart rate to systolic blood pressure; normal range, 0.5–0.7) can also be useful [81].

The evaluation of cardiovascular function is much more difficult. When available, echocardiography and ultrasound are the techniques of choice. Though requiring provider skills, these give rapid access to the volume status, cardiac function, and assessment of lung edema. Echographic assessment is relatively cheap, though involving some initial expenditure.

The decision to give fluids can be triggered by clinical signs of organ hypoperfusion and elevated lactate levels in the absence of raised jugular venous pressure. When a central venous catheter is in place, the CVP, $ScvO_2$, and $PvaCO_2$ values help to monitor the physiologic process and guide therapy. However, as reported above, CVP has its limitations, and the other indices indicate inadequate perfusion but not fluid responsiveness.

Table 3 Alternatives to the pulmonary artery catheter with special emphasis on techniques available in low-resource settings

Physical examination findings	Pathophysiology	Main interest/comments
Altered mentation[a] Skin abnormalities (cold and mottled skin)[a] Oliguria[a] Tachycardia Hypotension[b]	Signs of hypoperfusion	Occult hypoperfusion may be present despite normal vital signs and urine output
Shock index	Linear inverse relationship to SV and CO	Universally available/easy to calculate High value should probably trigger hemodynamic interventions
Peripheral pulses	If diminished suggests elevated SVR/low CO	Not in patients with severe vasoconstriction and/or arterial disease
Capillary refill time	Marker of peripheral perfusion	Easy access If prolonged (>4 s), related to increased morbidity and mortality
Laboratory tests		
pH (potential of hydrogen) BE (base excess) Anion gap	Markers for severity of tissue hypoxia	Surrogate for lactate in shock (especially hypovolemic) if no confounding factors (i.e., renal failure)
Hemoglobin	High levels suggestive of dehydration Very low hemoglobin levels may reflect the severity of bleeding	Marker of dehydation—many confounders Limited value in evaluating fluid responsiveness
Sodium Urea/creatine ratio Hemoglobin	Elevated serum levels indicate hemoconcentration	Markers of dehydration Limited value in evaluating fluid responsiveness
B-type natriuretic peptide (BNP)	Increase with myocyte distension caused by ventricular volume expansion or pressure overload	Differentiate heart failure from pulmonary causes of dyspnea Relatively expensive test
$ScvO_2$	Reflects an imbalance between DO_2 and VO_2	Decreased in low flow states or acute anemia Increased in distributive shock because of microvascular and/or cellular dysfunction
$PvaCO_2$	Linear inverse relationship to SV and CO	If >6 mmHg suggests that perfusion is inadequate If elevated along with high ScvO2 reflects microcirculatory alterations
$PvaCO_2/C\ (a\text{-}v)O_2$	Index of anaerobic metabolism	If >1.3 suggests under resuscitation Relatively complex to calculate
Serum lactate	Assesses DO_2/VO_2 balance	Increased in all types of shock Target for resuscitation Slow changes
Hemodynamic monitoring		
Jugular venous pressure (JVP)	High JVP may indicate hypervolemia, cardiogenic or obstructive shock, or RV dysfunction	Safety limit for fluid administration Limited value in evaluating fluid responsiveness
Central venous pressure (CVP)	Estimate back pressure for venous return, when elevated, results in elevated tissue capillary pressure and decreasing organ perfusion pressure	Extreme values are interesting but otherwise limited value in evaluating fluid responsiveness High values suggest RV dysfunction and/or hypervolemia
Arterial pressure—pulse pressure (PP < 40 mmHg)	Suggests stroke volume is low	Infusion of fluids if the patient can benefit from it, if signs of pulmonary edema are not present
Arterial pressure—systolic blood pressure	Seen as a reflection of the left ventricular afterload	Vasodilators decrease systolic BP and arterial wall stress and increase ascending aortic blood flow during late systole

Table 3 continued

Physical examination findings	Pathophysiology	Main interest/comments
Arterial pressure-diastolic blood pressure (DBP < 40 mmHg)	Suggests low arterial tone (especially in the presence of tachycardia)—important for coronary perfusion	Can be used as a trigger for giving vasopressors
PPV-dynamic indices based on pulse pressure	PPV > 13% suggests fluid responsiveness	Can be used as an indicator of fluid responsiveness, in the presence of fully controlled mechanical ventilation
Tidal volume challenge dynamic index based on pulse pressure	$\Delta PPV_{6-8} > 3.5\%$ suggests fluid responsiveness	Can be used as an indicator of fluid responsiveness, in the presence of fully controlled mechanical ventilation
Plethysmographic indices (ΔPOP/PVI)	Suggests fluid responsiveness	Signal significantly reduced by factors such as hypothermia, low cardiac output, and vasoconstriction
Chest radiography	Helps to evaluate the severity of lung edema—may help in the evaluation of a cardiac origin of shock/fluid overload	Lacks sensitivity and is related to interobserver variability
Basic bedside echocardiography	Comprehensive evaluation of CO and cardiac function (including response to therapy)	Training required Intermittent and somewhat time consuming
Lung ultrasound	B-lines are the sonographic sign of pulmonary congestion	Can be used for diagnosis and as safety limit for fluid administration

SV stroke volume, *CO* cardiac output, *SVR* systemic vascular resistance, $ScvO_2$ central venous saturation, O_2ER oxygen extraction rate, DO_2/VO_2 oxygen delivery/oxygen consumption, $PvaCO_2$ venoarterial PCO_2 gradient, *C(a-v)* O_2 arterial-venous O_2 content difference, *PPV* pulse pressure variation, ΔPPV_{6-8} change in PPV after increasing tidal volume from 6 to 8 ml/kg predicted body weight for 1 min, *ΔPOP/PVI* respiratory variation in pulse oximetry plethysmographic waveform amplitude and the pleth variability index

[a] Clinical windows of tissue perfusion

[b] Not mandatory for the diagnosis of circulatory shock

As both excessive and insufficient fluid administration can worsen outcome, it is important to identify fluid responders before giving fluids. The effect of inadequate fluid administration is probably even more detrimental in resource-limited areas. In African children with septic shock, mortality increased when fluids were given until signs of intolerance occurred [82]. Several strategies can be used to predict response to fluids. PPV nicely predicts fluid responsiveness and does not require specific equipment if an arterial catheter is used [83]. These can be automatically calculated by most bedside monitors. However, it is unreliable during low tidal volume ventilation [84], which is now routinely used in all critically ill patients. The 'tidal volume challenge' is a novel test that may help to circumvent this limitation [85]. This involves transiently increasing tidal volume from 6 ml/kg PBW to 8 ml/kg PBW for 1 min and observing the change in PPV (ΔPPV6–8). Plethysmographic indices of fluid responsiveness are non-invasive and quickly obtained [86]; however, the signal quality is critically dependent on the peripheral perfusion [87]. Of note, SV variations and derived variables are also present in acute cor pulmonale [88]. A passive leg-raising test can be used and has the advantage of avoiding these limitations, but is also somewhat cumbersome. It requires evaluating changes in cardiac output in relation to changes in arterial pulse pressure or, better, to changes in end-tidal CO_2 in intubated patients [89], or echocardiography or carotid/brachial Doppler, especially in emergency departments/wards, which usually have access to linear ultrasound probes.

Finally, studies are needed to evaluate whether bundles, protocols, and potentially telemedicine, would cost-effectively improve outcomes in limited-resource settings.

Putting it all together

As described in this article, there are many alternatives to the PAC. Each has its own interesting features and limitations. Instead of relying on a single technique, it is useful to combine different techniques and, even more importantly, to adapt the "package" of interventions to the patient's condition, taking into consideration the actual hemodynamic state and the likelihood of deterioration and comorbidities. As a first step, the clinical and biologic signs should be used to identify patients with impaired tissue perfusion. Whenever available, echocardiography should be performed as it provides a rapid and comprehensive hemodynamic evaluation. If the patient rapidly responds to therapy, either no additional monitoring or pulse wave analysis (allowing continuous monitoring in case potential degradation is anticipated) can be applied. If the patient does not rapidly respond to therapy or if complex hemodynamic alterations are observed, pulse

wave analysis coupled with TPTD is suggested, supplemented, of course, with regular assessment of clinical and biologic indices of perfusion and coupled, if needed, with repeated echocardiographic evaluation. When macrocirculation seems within reasonable goals and the metabolic indices remain altered, it seems reasonable to suspect microvascular alterations. While therapeutic options remain limited at this stage, the indication is that further attempting to increase CO is probably unnecessary.

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Compliance with ethical standards

Conflicts of interest
Daniel De Backer: Consultant to and given material for studies by Edwards Lifesciences. Jan Bakker: No conflict of interest. Maurizio Cecconi: No conflict of interest. Ludhmila Hajjar: No conflict of interest. Da-Wei Liu: No conflict of interest. Suzana Margareth Lobo: No conflict of interest. Xavier Monnet: Consultant to Pulsion/GETINGE, Munich, Germany. Andrea Morelli: No conflict of interest. Sheila Nainan Myatra: No conflict of interest. Azriel Perel: Consultant to Pulsion/GETINGE, Munich, Germany, and to Masimo Inc., Irvine, CA, USA. Michael R. Pinsky: Consultant to Edwards Lifesciences, Cheetah Medical, LiDCO Ltd., honoraria for lectures from Masimo Inc., Edwards LifeSciences, Cheetah Medical, and stock options with LiDCO Ltd., Cheetah Medical. Bernd Saugel: Collaboration with Pulsion Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board and received honoraria for lectures and refunds of travel expenses from Pulsion Medical Systems SE. BS received institutional research grants, unrestricted research grants, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA). BS received honoraria for lectures and refunds of travel expenses from CNSystems Medizintechnik AG (Graz, Austria). BS received research support from Edwards Lifesciences (Irvine, CA, USA). Jean-Louis Teboul: Consultant to Pulsion/GETINGE, Munich, Germany. Antoine Vieillard-Baron: Received a grant from GSK for conducting clinical research and is a member of its scientific advisory board. Jean Louis Vincent: No conflict of interest.

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