

Hemodynamic Monitoring in Critically Ill Patients with Sepsis

Chiarandini P¹ and Della Rocca G^{1*}

Department of Anesthesia and Intensive Care, University of Udine, Italy

***Corresponding author:** Della Rocca G, Department of Anesthesia and Intensive Care, University of Udine, Italy, Email: giorgio.dellarocca@uniud.it

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INTRODUCTION

Many hemodynamic monitoring systems are available in everyday clinical practice, and they can give information on different aspects of cardiovascular function. The better tools must be chosen taking into account the utility (more or less proven) of the information obtained versus the risks (invasiveness) for the patient and the resource available (costs) [1].

Nowadays a patient can be monitored with multiple hemodynamic devices depending on the stage of the critical illness, the severity of the organ failure, the comorbidities, and so on. Aim of monitoring is obviously to decrease morbidity and mortality for the single patient, remembering that every monitoring tool *per se* does not have a therapeutic effect but its usefulness depends on the knowledge and skill of the clinician, and that the availability of specific treatments algorithm and drugs makes the difference.

WHY SHOULD WE MONITOR A SEPTIC PATIENT?

Hemodynamic Derangements in Sepsis

Sepsis, defined as a severe infection with one or more life-threatening organ dysfunction, affects a large proportion of the critically ill population and is associated with considerable morbidity and high mortality rates. In most severe cases, i.e. when is associated with hypotension and increased lactate levels (septic shock), mortality can easily exceed 40% [2,3].

Sepsis proceeds as a continuum between the first sign of infection and the multi organ dysfunction, and as soon as the treatment of the infection, the source control and the supportive measures begins, as much as increase the probability to control the disease process and reduce death and complications.

One of the most frequent treatments in septic patients relies on correction of the hemodynamic derangements caused by the inflammatory process. The time course of the developing of the shock cannot be univocally defined in patients, and depend on different factors: the magnitude of the response, the virulence of the pathogen and the status of the cardiovascular system at the moment of the onset of infection. In last decades septic shock was defined as a state of acute circulatory failure, and the presence of hypotension (usually below 65 mmHg of mean arterial pressure) with or without a raise in lactates, as the main feature of the most severe form of sepsis [4]. This definition, although focusing on one of the most accessible hemodynamic variables at the bedside (arterial pressure), does not take into account the complexity of the process and the presence of an altered cellular metabolism caused by the reduction of blood flow, dysoxia and altered biochemical processes. These processes are present earlier than the manifestation of hypotension. The most recent definition of sepsis and septic shock, introduced the concept of severity of illness (enough severe to affect mortality) and in this way favoring a broader view than in the past to differentiate septic shock from cardiovascular dysfunction alone. Now the definition includes not only the presence of hypotension, but also the need of vasopressor to maintain an adequate blood pressure, and the presence of lactates over the normal range [2].

Hypotension, Vasodilation and Vasoplegia

In the septic patient, because the probable loss of autoregulation mechanism, an abnormal level of arterial pressure can be a marker of an increase in the severity of the disease toward a shock state, but can also be the result of a transient impairment of the circulatory system due to the presence of the infective process, the fever and fluid losses and this could determine a different treatment strategy.

Often at the base of the hypotension of the septic patient there is a vasodilation in a subject that is relatively hypovolemic. This is why in the definition of septic shock it's been added the concept of "adequate fluid resuscitation" to differentiate hypovolemia derived hypotension from hypoperfusion associated hypotension [4].

Although hypotension is not always correlated with hypoperfusion and no ideal level of arterial pressure is considered optimal, usually the targets for arterial pressure are a systolic > 90 mmHg or a mean > 70 mmHg. These numbers should probably be modified taking into account age of the patient and history of hypertension.

Vasopressors and fluids are the most used drugs to reach these goals. Both of them have adverse effects that must be considered. Excessive fluids are associated with edema formation which can theoretically worsen cellular hypoxia due to the increase in space between the red cells in the blood and the mitochondria, while vasopressors induce vasoconstriction that can contribute to alter the microcirculation, uncoupling the physiologic redistribution of blood flow to tissues and reducing cardiac output through an increase of the after load of the left ventricle [5]. Moreover vasoactive drugs have other metabolic and immune-modulating adverse effects. Recent multicenter trials have demonstrated that there is no advantage in mortality at 28 or 90 days in unselected septic shock patients to reach mean pressure values higher 65-70 mmHg, and probably this is the best target if there are no other target to look at (metabolic or flow related), or if the patient does not have a clear clinical sign of improvement or worsening at different arterial pressure levels [6].

The best vasopressor drug to increase pressure in septic patients is probably norepinephrine, since it has a lower impact than epinephrine in decreasing splanchnic circulation, and has lower arrhythmogenic side effects than dopamine [7].

Microcirculation

Microcirculation and its basic element “endothelium” is the largest organ in the body and can be considered as the system that surrounds cells and allows them to live.

A key molecule in the regulation and function of microcirculation is Nitric Oxide (**NO**) that is able to dilate capillary and then modify blood flow. NO production and metabolism has been proven to be altered in septic states, and it has been considered a target for drug intervention. At the moment no drug specifically targeted to interfere with production of NO, has been demonstrated to improve outcome [8]. For sure NO inhibitors like Methylene Blue are able to increase arterial pressure in cases in which high dosages of norepinephrine are needed, and this in some clinical situations can be helpful [9]. The presence of Microcirculatory alterations have been demonstrated in different organs and tissues during sepsis and septic shock, and between them, kidney, gut, liver and others.

An intriguing aspect of microcirculatory alterations in septic patients is that, despite the evidence of altered flow through capillaries, and the increase in concentration of molecules linked to dysoxia such as lactates, only rarely there is evidence of cellular death or necrosis [10].

Despite the fact that we still don't know if microcirculation alterations are the effect or a cause of organ dysfunction, it seems reasonable to balance the effect of any hemodynamic intervention also considering the effects induced on the microvascular network.

Heart failure: ventricular dysfunction in the septic patient

The classical hemodynamic picture of sepsis is characterized by a hyperdynamic state with *high cardiac output*. The reason for this stays in the reduced left ventricular after load caused by vasodilation and in the usually high heart rate of the septic patient. So the heart was believed to respond physiologically to changes in vascular tone and that it was not affected by the inflammatory process by itself [11]. In reality the heart, like all other organs, is not unaffected by the septic process, and now *sepsis-induced cardiomyopathy* is a clinical entity characterized by a left ventricular dilatation and depressed ejection fraction, that need at least 7-10 days to recover. When the heart dysfunction is particularly severe the clinical picture resemble a normal or hypokinetic state. In these cases inotropes may be considered to increase cardiac output. The sepsis cardiomyopathy must be kept in mind when therapeutic maneuvers, such as fluid challenges or vasopressors, are utilized to correct hypotension or hypoperfusion.

Sepsis also triggers Takotsubo cardiomyopathy (also called apical ballooning syndrome), that is characterized by a depression of the mid-to-apical segments of the left ventricle [12].

Echocardiography is the best tool to make diagnosis of decreased left (or right) ejection fraction, and to follow the recovery in time. A rise of B-type Natriuretic Peptide (**BNP**) is also associated with sepsis-induced cardiomyopathy, although it is not correlated with an increase in left ventricular filling pressures [13]. Changes in Troponin I levels instead, are frequently seen during septic episodes and can be due to acute coronary syndromes or renal failure, and so are not a marker of cardiomyopathy [14].

WHAT TO MONITOR IN A SEPTIC PATIENT?

From the Heart to the Capillary

As previously seen the hemodynamic changes caused by the infection and the associated inflammatory state are complex and involve almost all the components of the cardiovascular system. Despite this not all these modifications are present at the same time and at the same magnitude. When the intensivist faces the hemodynamic profile of a patient with a severe sepsis or a septic shock, he should try to improve perfusion or reverse hypoperfusion (the real goal of his therapy), correcting first the most probable aspect causing the symptoms, and bearing in mind that all therapeutic options he will use (drugs, fluids or whatsoever) will probably have a narrow risk/benefit ratio.

Fluid Status

In critically ill patients, fluid resuscitation is the first step in the treatment of hypovolemia and shock. The same has always been considered also for septic patients, and absolute or relative hypovolemia needs to be ruled out before start using vasopressors or inotropic agents.

Systemic infection triggers an inflammatory cascade that induce vasodilation, fluid leaks

through capillary and augmented losses through fever. So it is reasonable to think that one of the first possible causes of hypoperfusion can be hypovolemia.

And this is why the first therapeutic measure generally prescribed is an intravenous fluid load with crystalloids, as stated in the last SSC guidelines. The amount of the fluid load is not univocally determined, but a volume up to 30 ml/kg of body weight in 30 minutes is generally considered adequate [4].

The criteria to consider if this amount is enough to counter balance hypovolemia, should be evaluated on the reversal of the sign and symptoms of hypoperfusion (e.g. decrease of lactates, increase in urine output, increase in arterial pressure) or on the measurement of some *indexes of fluid responsiveness* that should avoid to reach the failure of the ventricles due to an excessive preload [15]. Unfortunately, this approach takes into consideration only the heart as a target of excessive fluid treatment. Instead a more positive fluid balance has been demonstrated to correlate independently with mortality at 12h and 4 days after the onset of septic shock [16]. A restrictive fluid approach has now gaining more and more support showing better outcomes as less fluid are infused in acute lung injury, postoperative patients, etc.

So in order to save as much fluids as possible, the best way to do it is through a fluid challenge/ fluid responsiveness test. The concept behind this approach is this: if a patient could benefit from an increase in blood flow, this can be achieved giving low volumes of fluids and seeing if there is an increase in cardiac output. If this happens, then one will check if the perfusion has improved and then decide to stop giving fluids. If not, more fluid challenges can be given until the resolution of the problem or the exhaustion of the possibility by the heart to increase flow increasing preload (stroke volume maximization).

A fluid challenge should be done with the lowest volume possible, and that's why colloids should be preferred, since they have a better effect of volume expansion with less passage in the extravascular space. However, in septic patients, synthetic colloids (starches, gelatins, dextran), have been demonstrated the potentiality to cause harm and are not more indicated, and so the choice should fall on human albumin. An accepted alternative could be crystalloids at the dose of 3 ml/kg given in a very short period of time (5-10 minutes).

An increase of cardiac output or stroke volume of 10-15 % is indicative of fluid responsiveness and then more fluids can be given in a controlled manner [17].

Arterial Pressure

In physiological conditions, at peripheral level, vascular resistances and consequently blood flow are subjected to auto regulation mechanisms that are able to diverge flow to organs or systems that need much oxygen. In case of sepsis, due to the high heterogeneity of involvement of organs and systems and to the inflammatory states in which they are, these autoregulation mechanisms fail and perfusion becomes more independent from pressure.

Moreover the effect of infusion of drugs to raise blood pressure can produce an increase in vasoconstriction in areas which are already hypoperfused not improving flow and worsening ischemia where ischemia is developing.

Non Invasive method of measuring Blood Pressure is based on oscillometry (**NIBP**) that can be performed semi-continuously. This method works well when mean arterial pressure is above 75 mmHg.

In case of shock, an invasive method should then be considered mandatory. Usually the site of choice for catheterization is at radial level because the risk of ischemia caused by thrombosis is low. Sometimes femoral artery can be preferred due to the increased size and to the fact that monitoring system requires a central pressure than a peripheral [18].

Cardiac Function

An increase of the cardiac output is the goal of most of the hemodynamic therapeutic efforts, and measurement of cardiac output *per se* is only of limited value, especially when is normal or high.

Many devices are nowadays able to measure more or less precisely cardiac flow. The difference between them relies on the possibility to measure other aspects of heart physiology like pressures or volumes. For instance, pulmonary artery catheter is able to provide direct measures of cardiac filling pressures, while echocardiography is able to visualize stenosis or insufficiencies of valves in both heart chambers.

So the importance in looking at the heart function in septic patients is based mainly on how much one can try to increase cardiac flow before and this depends on different aspects that include, previous cardiac diseases, the preload state of the patient, the inotropism of the myocardium and its adequate coronary flow, etc.

Oxygen Delivery and other Oxygen Derived Variables

Oxygen is the key molecule of life since it's at the heart of cellular respiration and energy production. It's utilization by the cell depends not only by the integrity of biochemical pathways and transport mechanisms from the blood to the mitochondria, but also from the amount of oxygen delivered from the heart to the capillaries. The relationship between Oxygen Consumption (**VO₂**) and Oxygen Delivery (**DO₂**) is usually biphasic, with the VO₂ independent from DO₂ at normal oxygen delivery values. This means that only for very low levels of DO₂ the cell change its metabolism to produce energy without oxygen (and producing lactates), and this can be done only for a short period of time. Since this is a very potential dangerous situation for the cell because it can be proximal to hypoxia and death, the oxygen delivery can be kept high enough by the increase of cardiac output (hemoglobin concentration cannot increase rapidly and oxygen saturation is usually at the top physiologically) or by the fact that oxygen extraction

can be increased almost three times. During sepsis the VO_2/DO_2 relationship curve is thought to become always linear with a VO_2 dependency also for high levels of DO_2 . This can explain why, at least at the beginning of sepsis, there is a compensatory response by the heart to increase oxygen delivery through the increase of cardiac output. If this increase is not enough, cells will extract more oxygen from the blood, reducing the amount of oxygen present in the blood that flows back to the heart (SvO_2). So, at least theoretically, when there is an initial ischemic state for an organ, this will be demonstrated by an abnormal low of SvO_2 , and when hypoxia starts developing a raise in lactate can be measured. This is what probably happens at the early phases of sepsis; while in the late phases cells lose the ability of utilize oxygen independently by the amount that is available.

In last fifteen years, hemodynamic therapeutic strategies aimed at increasing oxygen delivery targeted to SvO_2 (or its surrogate, $ScvO_2$), have been subjected to different and controversial results. The last trials published failed to demonstrate any mortality reduction in septic shock patients [19]. However, the goodness of this early-goal directed approach stays in its physiological rationale and more data are needed to definitely drop out this strategy.

HOW TO MONITOR A SEPTIC PATIENT?

Classically, hemodynamic monitoring devices can be divided in non invasive, minimally invasive and invasive. The concept of invasiveness is not clearly defined and depends on different factors that take into account risk of complications related to their use but also the discomfort that create to the patient. Moreover some “hemodynamic monitoring tools”, like heart rate and arterial pressure are usually considered “routine” for every ICU patient, while some are not strictly only hemodynamic, like SpO_2 or $EtCO_2$. A review of the “basic monitoring” of intensive patient is beyond the scope of this chapter, so we will consider only devices or techniques that can measure or estimate at least the cardiac output as a fundamental component of oxygen delivery.

Echocardiography

In last ten years, ultrasounds (US) have been increasingly used in ICU also by non radiologists. Routinely US examination of heart, thorax and abdomen has become standard of care for most intensivists. Although it depends a lot on the expertise of the operator and on the possibility to visualize the heart through the thoracic cage and the lungs, its execution, also in novice hands, can give valuable information in case of a septic patients [20].

On performing an echocardiogram the intensivist should assess the left and right ventricular cavity sizes and functions, the cardiac output, the presence of pericardial effusion and the fluid responsiveness in case of fluid challenge [21].

These tasks do not require the same skill, and some are quite easy to perform, such as cavity function and sizes, while others necessitate of much more training (cardiac output determination and fluid responsiveness assessment).

An another important advantage of echocardiography is the possibility to repeat the test as many times as necessary, evaluating changes induced by treatment maneuvers.

In a septic patient, with or without shock, the first thing to do is rule out the presence of hypovolemia (absolute or relative) and then see if a fluid challenge can improve peripheral perfusion.

In this view, the visualization of ventricular chambers can give an easy and fast way to determine if the patient needs fluids. For instance if the ventricle walls touch at the end of systole (kissing ventricle), then the patient can benefit of a fluid challenge. On the contrary, the presence of a ventricle with distended walls, especially on the right side, could indicate that a septic heart failure is ongoing.

The measurement of cardiac output by means of echocardiography needs the ability to use Doppler and to measure the left ventricle output flow, and require a higher degree of experience.

Non Invasive or Minimally Invasive Monitoring

In recent years, many mini-invasive methods of hemodynamic monitoring appeared on the market. They are based on different biophysical principles and most of them estimate cardiac output through the direct measure of another parameter (arterial pressure, CO₂ rebreathing, esophageal Doppler, etc) and assuming that the relationship between the cardiac output and the variable measured depends on factors that can be computed or estimated *a priori* (age, sex, arterial compliance, etc).

Each system developed has inherent strengths and limitations [22].

Pulse Contour Techniques (LIDCO TM Rapid, Most Care-CO, CNAP, Clear Sight/Physical, MASIMO, Flotrac)

Pulse contour techniques analyze the pressure in an artery over time to derive a waveform, and use this information to calculate cardiac performance. Changes in vessel diameter are assumed to reflect pressure changes resulting from a variable cardiac output. Most of them are based on a three-element model integrating aortic characteristic impedance, arterial compliance and systemic vascular resistance. Although these models work relatively well in stable patients, when a patient becomes unstable or when vasoactive drugs are being used, most models lack accuracy [23]. While fine-tuning of the algorithms being used in the monitoring devices try to improve efficacy, further steps need to be taken.

Esophageal Doppler Monitor (CardioQ ODMTM)

This method measures blood velocity in the descending aorta by means of a transducer emitted pulsed wave placed on an esophageal probe. As blood velocity changes with the pulsatility of flow, the integral of area under the velocity-time curve is used to calculate the stroke distance per heartbeat. By multiplying the aortic cross-sectional area by the stroke distance, the stroke volume is calculated [24].

Data obtained with this methodology in septic patients have been published, but the necessity of a stable and fixed probe in the esophagus is an important limit [25].

Bioreactance and Bioimpedance

The electric resistance of the thorax is determined by the amount of fluid (blood) inside, and changes of the volume of thoracic fluid (mainly the aortic blood flow), are proportional to the voltage measured by electrodes placed on thorax and neck surface. While bioimpedance measures changes in amplitude, the Bioreactance relies on the changes in signal frequency.

Invasive Monitoring

Cardiac output determined through the analysis of the thermo-dilution curve is considered to be the “gold standard” in clinical settings. To do this an injection port located as close as possible to the right heart, and a thermistor located downstream able to measure the thermal curve are necessary.

Since the 1970 the most used device to do it has been the Pulmonary Artery Catheter (**PAC**). For decades, it was the only catheter to directly measure cardiac output. Its complications are well known and nowadays is considered the most invasive hemodynamic monitoring tool in clinical practice. Despite this, it still has some advantages and indications since it can directly measure not only cardiac flow, but also pressures in heart ventricles, atria and pulmonary vessels.

However, there have been extensive debates around its widespread application triggered by an absence of studies demonstrating a clear outcome benefit as well as its risk/benefit profile [26].

The standard PAC is able to give only intermittent evaluation of cardiac output. But the presence of a thermic filament around the portion of the catheter passing through the right atria and ventricle can give a semi-continuous estimation of cardiac output that do not necessitate the injection of the saline bolus.

This catheter (Intellicath), coupled also with the heart rate, can also measure the Right Ventricular Ejection Fraction (**RVEF**) and the continuous assessment of right ventricular End Diastolic Volume (**cEDV**). These “volumetric” parameters can be used to determine the ability of the heart to manage an increase in venous return or preload.

The presence at the tip of the catheter of a sensor capable of measuring oxygen saturation can allow the continuous determination of the SvO_2 that is related to oxygen extraction and oxygen delivery.

One of the clinical problems related to the use of PAC stays in his passage to the right heart chambers and their valvular systems. The longer the catheter stays in place the higher the probability of lesions to the valves and of developing endocarditis.

To partially overcome this problem, two other hemodynamic monitoring systems able to measure CO directly have been developed. These systems (**PiCCO** and **LIDCO**), use an arterial catheter (femoral or radial) to determine the thermo-dilution curve, generated by the indicator (saline or lithium) injected in the vena cava. These systems are less invasive than the PAC, but maintain a good precision and accuracy of the CO determination, also through time. Moreover, coupled with a pulse contour technique, can give a continuous reading of cardiac flow without the loss of precision determined by changes in vascular compliance and resistance.

The fact that the thermodilution curve is determined after the bolus passed through the right heart, the pulmonary circulation, the left chambers and the descending aorta, led the possibility to estimate also volumes of blood presents in the pulmonary circulation and all cardiac chambers. The measurements of Global End-diastolic Volume (**GEDV**) and Intrathoracic Blood Volume (**ITBV**) have been demonstrated to correlate with classical preload indexes, and can be used as surrogate markers of preload [27].

The usefulness of PiCCO derived variables has been tested in many septic patient trials. However, as for PAC, no PiCCO associated treatment algorithm has been demonstrated per se reduce mortality or morbidity of septic shock patients [28].

Derived Based Treatment Algorithm

Sepsis and septic shock are systemic complex syndromes that come from the interaction between an infectious organism and the inflammatory response triggered by the immune system. The hemodynamic profile of these patients is characterized by multiple possible changes that can range from a hypodynamic state of oxygen delivery dependence (early) to a hyperdynamic state where oxygen consumption becomes independent of oxygen delivery (late). The core of the problem stays in the endothelium dysfunction with microvascular perfusion alterations. However the possibility to directly diagnose and manipulate perfusion at this level is scarce and limited. So the best supportive hemodynamic treatment, still remain at a macrovascular level although the integration of vascular parameters with metabolic indexes of perfusion (such as lactates) and oxygen utilization variables (such as ScvO₂) remain the best standard of care.

When a septic patients needs to be transferred to ICU is because the intensivist recognized that infection has starting evolving to a systemic and poor controlled disease and/or the organs and systems failure are becoming life threatening.

Much of these patients will have an impairment of cardiovascular function that need to be treated with the aid of some monitoring tool. There is no consensus on what's the best choice. A protocolized approach (early goal directed) seems the best option also if no single target (flow vs. volumes vs. pressures vs. metabolic) has been demonstrated superior at the moment.

For sure the basic hemodynamic monitoring for an intensive care patient consists of an arterial line and a central venous catheter (besides EKG and urinary output) (*Level 1*). These will allow to

define if the patient is hypotensive, if it's seriously hypoperfused (lactates) and if he's developing an oxygen debt (ScvO_2).

The goal of the treatment then will be to try to bring back all these parameters to normal values. Some fluids could help to do this. How much and what type of fluids will be based on a clinical judgement. At this point an echo evaluation of the heart could better define the necessity of more fluids or the risk of an excessive over hydration. If targets won't be reached (the patient is still hypotensive, oliguric, etc), then a step up in monitoring, will be necessary (*Level 2*).

To follow a stroke volume maximization strategy (that means that we think that fluid challenges can improve cardiac output and so oxygen delivery), we need to measure stroke volume or cardiac output. Considering the patient a septic one, a calibrated device will be probably the best tool. If the patient for some reasons is intubated and paralyzed, also dynamic indexes obtained from uncalibrated techniques, such as Pulse Pressure Variations (**PPV**) or Stroke Volume Variations (**SVV**), could be utilized, as long as esophageal Doppler. But usually this is not the case, since nowadays few septic patients have indications to be paralyzed in intensive care for long periods.

The choice of which calibrated device is better will depend on different factors. LiDCO does not need a femoral artery and a central venous catheter, but the indicator for thermodilution is lithium that cannot be repeated as often as saline. Moreover, apart from SV, other parameters are not so well validated as those measured by PiCCO. Instead PiCCO system can give, besides cardiac output, also volumetric parameters (**ITBV**, **GEDV**, etc) and an estimation of pulmonary damage (**EVLW**).

Echocardiography, at this level, can also be useful, since it's non invasive and easily repeatable. Probably the skillness requested to interpret US will be higher, since the magnitude of alterations visible will be attenuated.

With this hemodynamic monitoring setting the intensivist will be able to titrate all therapies aimed at sustain cardiovascular function (fluids, norepinephrine, blood, etc) at their maximum efficiency for most of the septic patients.

An increase in invasiveness in monitoring will then be justified by the presence or by the development of particular clinical situations such as heart failure or severe ARDS.

In these cases an advanced or a normal PAC will give the possibility to monitor in a better way heart function and pulmonary pressures (*Level 3*).

Therapies aimed at reduce pulmonary hypertension, or improve function of a failing ventricle will be tailored at their best. The heart at this point has become a major problem, and echocardiography could help to define better the clinical picture. Competencies needed to do it are surely far from a basic level.

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