Mean Arterial Pressure: Therapeutic Goals and Pharmacologic Support

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Early goal-directed therapy in sepsis, including the optimization of hemodynamic parameters, has been demonstrated to improve end points of resuscitation, limit organ dysfunction, improve mortality, and contribute to decreases in resource consumption.1 The Surviving Sepsis Campaign2 targets central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation (ScvO2) as guides for resuscitation.3 These measurements, achieved with fluid resuscitation and vasoactive medications, are guidelines for goals of resuscitation, and help to guide the clinicians’ decision-making regarding the success of such measures. Further, it has been demonstrated that the achievement of supranormal physiologic parameters, compared with the normal values as the targets of resuscitation, leads to an increase in mortality.4,5 A MAP greater than or equal to 65 mm Hg is imperative to maintain perfusion pressure and adequate flow at the arteriolar level. At pressures below this number, autoregulation can be dysfunctional in many tissue beds.2 Patients with septic shock require vasoactive therapy to achieve adequate tissue perfusion.6,7 The use of norepinephrine is recommended to maintain MAP of 65 mm Hg, and has been shown to preserve tissue perfusion.7 Although adequate volume resuscitation should be achieved before instituting vasoactive medications, their use may be required simultaneously with volume resuscitation early in the resuscitation to escape patient demise. The Surviving Sepsis Campaign guidelines are listed in Box 1.2

Therapy for septic shock should include the maintenance of organ perfusion and cardiac output; infectious source control; and, when possible, an interruption of the cascade of events propagating the septic state. Organ perfusion must be maintained during the administration of antibiotics, procedures to achieve surgical drainage, and other interventions. Therapeutics must be targeted at circulatory support from the
outset of intervention. Although the phenomenon of organ dysfunction in sepsis is complex, the maintenance of organ perfusion in the septic state depends partly on MAP. Maintenance of MAP as a therapeutic target for vasoactive medications is a mainstay in the care of the septic patient.\(^1\),\(^8\)

This article identifies the nature of arterial pressure and the maintenance of blood flow and cardiac output during sepsis and septic shock, and suggests means of supportive measures when possible.

**DEFINING MAP**

Circulatory pressure is derived from the ejection of blood from the left ventricle. Ventricular acceleration of blood into a normal arterial system results in elastic distention of the vessel walls. Potential energy is generated by this elasticity and subsequent recoil, in a normal arterial system, resulting in continuous pressured flow of blood, even during diastole.\(^9\) Blood pressure is measured traditionally as a systolic number, the highest pressure occurring as a result of left ventricular contraction, over a diastolic number, which is the result of continuous forward flow during the period of cardiac filling and rest. The MAP is not an arithmetic mean, and instead is derived to represent the proportion of time in systole and diastole.\(^10\)

The vascular circuit maintains blood pressure with the cardiac function acting as pump, and the blood vessels serving as conduit. The circuit is composed of arteries, capillaries, and veins. The pulmonary circuit is similarly composed, but is not discussed here. The flow through these conduits at rest is near 5 to 8 L/min. The flow is dependent on the pressure gradient between both ends of the circuit, and the resistance to flow within each conduit.

The MAP can be measured by invasive or noninvasive monitoring,\(^9\) but is defined as the area under the blood pressure curve divided by the time of the cardiac cycle:

\[
\text{MAP} = \int P \, dt / \Delta t
\]

An approximation can be made of the MAP from the systolic blood pressure and diastolic blood pressure:

\[
\text{MAP} = (2 \times \text{DBP} + \text{SBP}) / 3
\]

where DBP is the diastolic blood pressure and SBP is the systolic blood pressure. As described previously, however, this formula approximates a MAP, and depends on normal physiology of the ratio of time in each portion of the cardiac cycle. The

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**Box 1**

The Surviving Sepsis Campaign guidelines

1. MAP maintained \(\geq 65\) mm Hg.
2. Use of norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available).
3. Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin (0.03 U/min) may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.
4. Epinephrine is the first chosen alternative agent in septic shock, which is refractory to norepinephrine or dopamine.
formula assumes a resting heart rate of 60 beats per minute. At this rate, diastole occupies two thirds of duration of the cardiac cycle. In normal physiology, the heart rate is unfixed and varies greatly during the septic state. Patients with heart rates greater than 100 beats per minute may have diastole lasting for less than half the cardiac cycle. MAP is then falsely elevated by this formula, and organ perfusion may be ineffective despite a measured MAP within a target range. Additionally, MAP is maintained at the aortic and arterial level, but as the intravascular volume progresses toward arterioles and capillaries, a significant pressure gradient exists.9

Blood flow through the circuit can only occur if a pressure gradient exists. CVP is 0 to 4 mm Hg, whereas the aortic MAP is around 70 to 90 mm Hg. This difference produces a pressure gradient from central arteries, dispersing the pressure through every patent vascular network, down to the value of the CVP. The rate of flow is determined by the degree of gradient between tissue beds, not by only the inflow and outflow absolute values.

**MONITORING THE MAP**

The first measurement of arterial pressure was made by Reverend Stephen Hales in 1731. Reverend Hales' rudimentary but effective measurement was performed in an equine artery cannulated with a goose quill, which was in turn connected to an 8-ft glass column of water. This methodology was impractical, but demonstrated pressure was present within the circulatory system.11 In 1847, Carl Ludwig’s kymograph recorded human blood pressure invasively. The device featured a u-shaped manometer fixed to a brass pipe. A float would sketch a rudimentary blood pressure curve on a rotating drum, which became the first blood pressure recording device. In 1855, Karl Vierordt demonstrated with an inflatable cuff that pressure in a human artery could be obliterated. Just a few years later, Etienne Jules Mary and Samuel Siegfried Karl Ritter von Basch independently contributed to the sphygmomanometer. The pressure required to obliterate pressure in an artery was measured and recorded. The devices were inaccurate, but the largest advance came with Scipione Riva-Rocci, who demonstrated the device using mercury as a measuring fluid. He proposed using the sphygmomanometer with distal palpation in 1896. Korotkoff, in 1905, proposed the use of auscultation in addition to sphygmomanometry. These techniques were simple, safe, and effective. Although the medical community was initially reluctant to adopt routine blood pressure monitoring, by 1930 it had become the standard of care.12

By the 1960s, the standard measurement of blood pressure was by mercury sphygmomanometer. Subsequently, continuous intra-arterial monitoring was reintroduced with electromechanical transducers replacing Hales’ glass column.

MAP may be measured or estimated. Most electronic recording devices measure the MAP by integration of the area under the pressure curve and division by the cardiac cycle duration. This provides far more accurate a measure, because the estimation method, mentioned previously, does not provide for variation in the duration of the cardiac cycle.

**Noninvasive Monitoring**

In most circumstances, blood pressure is measured by manual or automatic noninvasive sphygmomanometry. Also in most situations, auscultation, palpation, and oscillometry measurements coincide, but systolic pressures measured indirectly may be up to 20 mm Hg lower than invasive monitors demonstrate, and diastolic pressures may be higher than invasive pressures. The noninvasive monitors also leave to chance the operator variability inherent to human interventions.13,14
Noninvasive monitoring devices use an air bladder to exert pressure in a cuff wrapped circumferentially, usually on the upper arm, measuring pressure transmitted through the brachial artery. The air bladder is positioned directly over the artery. The cuff is then inflated to a pressure above the disappearance of the distally palpated pulse. When positioned properly, inflation of the air bladder compresses the artery against the adjacent bone, decreasing and eventually stopping the flow of blood. This should result in both the absence of distal palpable pulsations and the absence of Korotkoff sounds, which are low-frequency sounds occurring during the occlusion of flow. The cuff is then deflated during auscultation, allowing for gradual return of flow. Turbulent flow of blood is restored as the cuff deflates, and sounds return, noted by the examiner or the device. In patients with normal physiology, vibrations associated with turbulent flow result in tapping Korotkoff sounds, correlating with systolic pressure. As the pressure of the cuff continues to decrease, more flow returns and Korotkoff sounds continue in a deformed blood vessel, and the character of the sounds develops from “tapping” to “popping,” and as the pressure approaches diastolic pressure, the sounds become muffled and eventually disappear. The disappearance of sound correlates with diastolic pressure. This method, despite astounding advances in technology, survives today as the most common method for deriving blood pressure.\textsuperscript{15}

Currently, most hospitals use automatic oscillometric machines to acquire blood pressure measurements. In turn, these machines calculate the MAP by the estimation formula mentioned previously, rather than by derivation. Machines can be calibrated to repeat the measurement at intervals, and are widely used in operating rooms, hospitals, and intensive care units around the world.

Although the noninvasive method is quite safe, there are pitfalls, including reasons for falsely elevated or falsely diminished measurements. A cuff that is inappropriately small may render a falsely high blood pressure reading. Also, obesity and measurements taken with the arm lower than the phlebostatic axis may contribute to falsely high readings. Similarly, falsely low readings can be obtained from too large a cuff or from the arm being measured too high above the phlebostatic axis. Human error may also contribute, with misinterpreted sounds, noisy environments, and artifact contributing to falsely high or low measurements.

**Invasive Monitoring**

Patients with septic shock, sepsis, or those who have the potential for sepsis should be monitored continuously and with invasive monitoring. The choice of catheter is a concern when monitoring blood pressure. According to the Poiseuille-Hagen formula, flow is directly proportional to radius, and inversely proportional to length and to fluid viscosity. This means that as the lumen diameter decreases, and as the length or viscosity increase, the flow diminishes. In the physiologic milieu of a septic patient, peripheral vasoconstriction provides an incremental increase in systemic blood pressure, but eventually the lumen diameter decreases to the point of flow insufficient for organ perfusion, and end-organ injury occurs. Similarly, the catheter chosen to measure pressure invasively contributes to the value monitored. Resistance in a system is the mathematical inverse of flow. Flow is expressed as:

\[
Q = \frac{\pi r^2}{8 \eta L}
\]

where \( \eta \) is the fluid viscosity, \( L \) is the length of the tube, and \( r \) is the radius.

It is imperative at this juncture to mark a distinction between pressure and flow. The use of vasoconstrictors to increase blood pressure in septic shock is widely
acceptable, but the vasoconstrictive effects of the agent chosen may also be the culprit in limiting blood flow at the end-organ level. Quite often, demonstration of an adequately maintained target MAP does not translate into organ blood flow.

Invasive monitoring is the most reliable method of continuous monitoring, and offers the advantage of relatively pain-free and low-risk access for blood sampling. Fluid-filled electronic monitoring is the most commonly used device for measuring blood pressure directly.

The fluid-filled system is composed of a catheter, a fluid-filled conduit, a transducer, an amplifier, and a recorder-monitor. The catheter, placed within a blood-filled vessel, can transmit the pressure through a static column of similar fluid, usually a crystalloid, to reach a transducer. The transducer converts the detected pressure into an electrical signal, which is delivered to the amplifier and to the monitor for display.

**MAP AND THE PHYSIOLOGY OF SEPSIS**

Intrinsic mechanisms to increase systemic blood pressure are the result of vasoconstriction by the catecholamine effect. The increase in measured blood pressure incompletely reflects perfusion pressure in different tissue beds. The resistance to blood flow in each tissue is in constant flux, changing in response to these intrinsic and other extrinsic phenomena. Poiseuille’s law describes resistance to laminar flow in a rigid tube:

\[
R = \frac{8\eta L}{\pi r^4}
\]

where \(\eta\) is the viscosity, \(L\) is the length of the tube, and \(r\) is the radius. Applied to the vascular system, the resistance in this simplified representation depends both on the blood composition and on the characteristics of the tube, or the blood vessel itself. Resistance is subject to viscosity changes, caused by hematocrit and protein concentration changes, and vessel radius, which is under autoregulatory and endogenous nervous system control. Poiseuille’s law provides only an approximation of resistance, however, because blood vessels are not rigid, flow is not laminar, and distribution of flow is not uniform.

Blood vessel radius, especially of the arterial tree, is the primary variable in the regulation of blood pressure. The resistances of the coronary, cerebral, and renal vascular beds are primarily controlled by autoregulatory means, and are less contributory to systemic vascular resistance. Most of the control is the arterial diameter in mesenteric, cutaneous, and skeletal muscle vascular beds. This blood vessel radius is under particularly influential control of circulating hormones, especially epinephrine, norepinephrine, angiotensin II, and vasopressin.9

**PHARMACOLOGIC SUPPORT OF MAP IN SEPSIS**

Support of septic patient begins with an adequately secured airway, appropriate ventilation parameters to optimize oxygenation and ventilation, and aggressive support of end-organ perfusion. Source control must be considered from the onset of interventions, and broad-spectrum antimicrobial coverage instituted. Although adequate volume resuscitation is imperative to the maintenance of organ perfusion in shock, refractory patients may require the use of vasopressors early or even from the initiation of care, concomitant with aggressive fluid resuscitation. Resuscitation end points may not be necessarily discrete; instead, appropriate goals of resuscitation target interventions toward restoration of tissue perfusion, and subsequent resuscitation is tapered to maintain, and not overshoot, those goals. Signs of adequate resuscitation,
according to the Surviving Sepsis Campaign, include an appropriate volume resuscitation to a CVP between 8 and 12 mm Hg, appropriate perfusion pressures demonstrated as MAP greater than 65 mm Hg, evidence of organ perfusion including urine output above 0.5 mL/kg/h, and evidence of adequate oxygen use with a superior vena cava oxygen saturation above 70% or mixed venous oxygen saturation greater than 65%.1,16

These end points of resuscitation in sepsis have been widely discussed and reported. The goals of therapy are to eliminate the source of sepsis, control its influence on the cascade of events leading to sepsis, and support the organism through these events. The optimum level of blood pressure is still unknown. The target of 65 mm Hg translates to higher perfusion pressures, and is thought to be the most optimum of goals.7,16,17 Vascular tone is mediated by three interwoven systems, each of which is affected by sepsis: (1) the sympathetic nervous system, (2) endogenous vasopressin, and (3) plasma angiotensin. The goal of pharmacotherapy for septic shock is to increase perfusion pressure to a point where blood flow is optimized.

Sympathetic tone can be restored with exogenous adrenergic agonists and the vasopressin repleted. Vasodilatory shock is a complex interaction between vasodilation, relative and absolute hypovolemia, myocardial dysfunction, and altered perfusion, each of which may be attributed to the systemic inflammatory response to injury.18,19 Many vasoactive agents have come in and out of fashion since the mid-twentieth century. Few randomized controlled trials exist to demonstrate their efficacy and contribution to improved outcome.20 Further, the Cochrane Database of Systematic Reviews describes that sufficient evidence is not yet suited to inform clinical practice absolutely, and that one particular vasopressor is no better than other agents in treatment of fluid-refractory shock.20

Agents useful in septic shock are described next. Many agents are available, each with its unique profile of effects.

**Norepinephrine**

Norepinephrine is a potent α-adrenergic agonist and less potent β-adrenergic agonist. It is useful to increase MAP in patients with hypotension caused by sepsis.21 Norepinephrine is equivalent in effect on increasing MAP,6,22,23 oxygen consumption, and oxygen delivery compared with other catecholamine pressors. At least one study has suggested that norepinephrine has greater potency compared with dopamine and more substantially improves the hemodynamic parameters of shock.

Martin and coworkers24 in a small randomized study of patients with hyperdynamic sepsis observed that 93% of patients receiving norepinephrine (1.5 ± 1.2 μg/kg/min) had normalization of MAP compared with only 31% who were receiving dopamine (10–25 μg/kg/min). In addition, norepinephrine has been shown to be effective rescue therapy when other catecholamine pressures have failed to maintain MAP. In one recent study, Martin and colleagues25 have suggested that norepinephrine use in patients with septic shock is also associated with a reduced mortality rate (relative risk = 0.68; 95% confidence interval, 0.54–0.87) compared with those patients treated with other catecholamine pressors. The etiology of the mortality difference is unclear but may relate to the side effect profile of norepinephrine compared with other agents.

Despite its greater potency and vasoconstricting potential, end-organ damage may be less prevalent in septic patients treated with norepinephrine compared with those treated with other catecholamine pressors. The addition of norepinephrine to other catecholamine pressors was observed by Redl-Wenzl and others to increase urine output and creatinine clearance.24 The mechanism is unclear but may be secondary to vasoconstriction of the efferent arteriole of the glomerulus, which leads to increased
filtration through the kidney. Unpredictable effects occur in the splanchnic circulation with some patients developing ischemia secondary to vasoconstriction. Preservation of cardiac output with the use of norepinephrine (and ionotropes), however, may preserve splanchnic flow. In addition, gastric pH has been observed to increase (not decrease) in septic patients treated with norepinephrine alone. As a result of improved end-organ blood flow, Martin and colleagues\textsuperscript{24} observed reduced lactate levels after treatment (4.8 ± 1.6–2.9 ± 0.8 mmol/L), suggesting improved tissue oxygenation and lactate clearance, the latter of which has been associated with improved survival.\textsuperscript{3}

Although the achievement of supraphysiologic MAP has been associated with increased mortality, evidence exists that increasing norepinephrine doses benefits tissue oxygenation.\textsuperscript{4,5,25} Jhanji and colleagues\textsuperscript{25} recently demonstrated that patients with septic shock had an increase in global oxygen delivery, cutaneous microvascular flow, and tissue oxygenation increasing MAP with norepinephrine. Although the effect was demonstrated in a small number of patients, and the incremental increase in oxygenation was of questionable clinical significance, if oxygen delivery and use are the answers to the morbidity of sepsis, these small increases may be useful. Further work is required.

**Epinephrine**

Epinephrine is also a potent $\alpha$-adrenergic and $\beta$-adrenergic agent that contributes to increasing MAP by both an increase in vascular tone and an increase in cardiac index. Epinephrine increases the delivery of oxygen to organ beds, but the use of epinephrine can increase oxygen consumption. The administration of epinephrine can treat hypotension resistant to other agents, but it should be considered a second-line agent because of its effects on splanchnic circulation and increases in lactate concentration. Because epinephrine is a potent $\beta$-adrenergic agent, tachyarrhythmias are often a complication.

**Vasopressin**

Vasopressin is a peptide hormone synthesized in the hypothalamus and transported to and stored in the pituitary. Vasopressin is released in response to decreased blood volume and osmolality. Vascular smooth muscle cells are directly affected by vasopressin through V1 receptors, and also acts to enhance the vascular response to catecholamines.\textsuperscript{26}

Under nonseptic conditions, vasopressin has little effect on blood pressure. During hypovolemia, it may prevent aberrancies in the vascular response to shock.\textsuperscript{22,27} The Vasopressin Vs Norepinephrine in Septic Shock Study reported there was no difference in 28-day mortality in groups with septic shock treated with each agent. Vasopressin fared better in a subgroup analysis of less severely affected patients. Further, vasopressin added to norepinephrine in a moderate dose (0.03 U/min) is as safe and effective as norepinephrine alone in fluid-resuscitated patients with septic shock. In this setting, patients may benefit from lower doses of norepinephrine with vasopressin, than with higher doses of norepinephrine alone.

**Phenylephrine**

Phenylephrine is a selective $\alpha_1$-adrenergic agonist, which mediates elevation in MAP by vasoconstriction. Phenylephrine has relatively selective vasoconstrictive effect, without direct inotropic activity. Although this makes it an attractive agent in the management of vasodilatory shock, caution must be observed in its use because of the potential to reduced cardiac output in this population.\textsuperscript{6} Without $\beta$-adrenergic
agonism, there may be a role for phenylephrine in patients with tachyarythmias related to other vasopressors, but its role in septic shock has not been extensively studied.

Increased doses of phenylephrine demonstrated an increase in MAP without a significant increase in cardiac index. Phenylephrine may be of selective use in small doses, and for unsustained use. If oxygen use is unaffected, then perhaps phenylephrine requires revisitation as an option in the septic patient. Linear increases in MAP without significant increases in cardiac index have been demonstrated in a study of septic patients, but these increases were met with unpredictable oxygen delivery and use. Increased doses of phenylephrine demonstrated an increase in MAP without a significant increase in cardiac index. Phenylephrine may be of selective use in small doses, and for unsustained use. If oxygen use is unaffected, then perhaps phenylephrine requires revisitation as an option in the septic patient. Linear increases in MAP without significant increases in cardiac index have been demonstrated in a study of septic patients, but these increases were met with unpredictable oxygen delivery and use.23

Dose-response studies are required to safely administer phenylephrine routinely.

**Dopamine**

Dopamine is the precursor of norepinephrine and epinephrine and has well-known distinctly dose-dependent effects. At doses of less than 5 μg/kg/min, dopamine receptors are activated with renal and mesenteric vasodilation. An increase to 5 to 10 μg/kg/min results in β1-adrenergic receptor stimulation and an increase in inotropic and chronotropic effect. At doses greater than 10 μg/kg/min, α1-adrenergic effects predominate, with vasoconstriction and increased MAP. Dopamine increases MAP in septic patients who remain hypotensive after volume resuscitation, but oxygen consumption may be affected adversely.24

The use of dopamine in septic shock may be optimal in patients with cardiac dysfunction. Tachycardia and a propensity for arrhythmias more than other agents make dopamine a good choice in the appropriate circumstance.

**REFERENCES**