AN OVERVIEW OF THE PATHOLOGY REQUIRING VASOACTIVE DRUG TREATMENT

Circulatory shock occurs when the cardiovascular system fails to maintain adequate cellular perfusion and delivery of oxygen and other nutrients which results in subsequent cellular and organ dysfunction. There are two main presentations by which shock is classified: one is characterized by decreased cardiac output, low blood pressure and profound vasoconstriction and the other one by altered flow distribution, vasodilation, and diminished blood pressure with normal, increased or decreased cardiac output. Table 1 summarizes these categories along with the most frequent encountered clinical situations for each. The etiology of distributive shock is most frequently sepsis, but any kind of circulatory shock could eventually lead to this pathophysiologic presentation.

END POINTS OF RESUSCITATION AND MONITORING

The benefit of treatment for shock is evaluated by various tools, a valuable one being bedside clinical assessment. In the absence of an arterial line, the systolic blood pressure (SBP) must be measured, with a goal of greater than 90 mmHg. Electrocardiogram (ECG) monitoring may unveil arrhythmias or a feared circulatory shock complication, myocardial ischemia. Signs of volume repletion include physiologic diuresis of at least 0.5ml/kg/h and capillary refill less than 2
seconds. Peripheral perfusion reflected in the skin and mucous aspect can be assessed on visual inspection. Sensorium may be clouded or altered in shock states, especially in the pediatric population.

Blood pressure should be followed by continuous monitoring if possible. Mean arterial pressure (MAP) is a reliable parameter in shock, and a goal of greater than 60 mmHg is considered optimal; animal studies have shown that if this goal is not achieved, the auto regulation in most organs is abolished. A small prospective clinical study revealed that increasing MAP from 65 to 85 mmHg does not significantly affect systemic oxygen metabolism, skin microcirculatory blood flow, urine output or splanchnic perfusion. Signs of MAP fluctuation with mechanical ventilation indicate a hypovolemic state.

Intravascular volume status needs to be evaluated regularly during treatment because the capacitance of vascular beds varies widely during the evolution of circulatory shock. Unfortunately, invasive monitoring techniques may be both costly and dangerous. A large retrospective analysis conducted in five US teaching hospitals on 5735 patients revealed that right heart catheterization is associated with increased mortality, morbidity and cost of care. Non-invasive monitoring with esophageal Doppler monitoring or thoracic electrical bio-impedance is gaining favor. Bedside echocardiography and evaluation of cardiac output (CO) is useful in distinguishing shock due to pulmonary embolism, myocardial infarction or hypovolemic. There is no demonstrated benefit in increasing cardiac index to a supra-physiologic level.

Mixed venous oxygen saturation (SVO$_2$) and central venous oxygen saturation (ScVO$_2$) are now common measures in septic shock resuscitation. SVO$_2$ requires a right heart catheter in place, and the goal is normally over 65%. ScVO$_2$ can be measured either continuously or intermittently via a central line, and it is the parameter used by Rivers and his colleagues in their early-goal directed therapy (EGDT) study; subsequently it was adopted as a recommendation by the Surviving Sepsis Campaign. The EGDT study was designed to resuscitate patients within the first 6 hours of a diagnosis of septic shock. The difference between the standard therapy arm and the EGDT arm in the study was the addition of a ScVO$_2$ goal to MAP, diuresis and CVP end points of resuscitation. If the ScVO$_2$ remained <70% after appropriate fluid resuscitation and vasopressor use, transfusions were administered to reach a target of 30% hematocrit, followed by dobutamine administration. With this approach mortality decreased significantly from 46.5% to 30.5%. There are at least 2 publications that question whether ScVO$_2$ is a good estimate for SVO$_2$ and oxygen demand (VO$_2$). A confirmatory multicenter study, Protocolized Care for Early Septic Shock (ProCESS) is currently being conducted by the US National Institutes of Health.

Improvement of tissue hypoxia is an unequivocal end-point of resuscitation, but it is difficult to assess. Lactate level is a surrogate parameter for tissue hypoxia although it better reflects cellular metabolism impairment than hypoperfusion. A lactate level lower than 2 mmol/l is a valuable prognostic factor and should be assessed repeatedly since the lactate level trend is more important than a single value. More than a decade ago, Bakker published a study that suggested the lactate level is a better predictor of outcome in septic shock than oxygen derived variables. In cases of respiratory or liver failure lactate values are increased. Lactate from Ringer's solution is rapidly metabolized in blood, so it can be used in sepsis for fluid replacement without affecting serum lactate levels. Although it has been studied for more than two decades, tissue oxygen saturation (StO$_2$) evaluated by near infrared spectroscopy as an end point of resuscitation is still a developmental technique.

The splanchnic circulation is affected by hypotension and vasoactive drug therapy. Gastric tonometry, which provides carbon dioxide partial pressure (PCO$_2$) and the gastric-arterial difference (PCO$_2$ gap), is used
for the evaluation of hepato-splanchnic ischemia. Although these parameters are frequently collected for research purposes they have resulted in contradictory results and are seldom encountered in clinical practice. Gastric intra-mucosal pH (pHi) calculated with the aid of arterial bicarbonate has also failed to become a routine end point for resuscitation, because arterial bicarbonate is a global marker of perfusion. Recently sublingual capnometry has gained more interest because it provides a reliable measure of PCO₂ which correlates with gastric PCO₂, blood lactate and SVO₂.

Standard markers of perfusion used in clinical practice for monitoring resuscitation results include: arterial blood gases with acid-base status, serum electrolytes (Na, K, Cl, Ca), renal function (BUN, creatinine, creatinine clearance), coagulation disturbances (INR, platelet count), liver function (AST, ALT, LDH, bilirubin), and gut abnormalities (malabsorption, ileus).

**ROLE OF RECEPTORS IN THE ACTION OF Vasoactive Drugs**

Vasopressors act either on adrenergic receptors (alpha and beta), dopaminergic (DA₁, DA₂) or vasopressin receptors (V₁). Inotropes exert their effects by stimulating beta adrenergic receptors, but some of them (phosphodiesterase inhibitors and levosimedian) effect KATP channels, and dampen the degradation of cyclic AMP or promote the sensitization of troponin C for calcium.

Table 2 summarizes the classification, effects and location of the adrenergic, dopaminergic and vasopressin receptors. Alpha-1 receptor acts on a G protein which causes an increase in calcium and stimulation of protein kinase C via phospholipase C.

Beta-1 receptor activates protein kinase A, via cyclic AMP increase, eventually leading to the enhancement of the intracellular calcium concentration. Both β-1 and α-1 receptors promote contractility by providing increased calcium concentration required for actin-myosin interaction. Vasopressin 1 receptor stimulates calcium release by activation of phospholipases and determines vasoconstriction in most vascular beds, except pulmonary where it causes a release of nitric oxide (NO) and vasodilatation. Levosimedian is a novel inotropic agent that sensitizes troponin C to calcium and thus enhances actin-myosin interaction in a manner dependent on calcium concentration, promoting an increased contractility in systole with low energy cost.

**VASOPRESSOR USE IN THE ICU: Dopamine**

Dopamine, the natural precursor of norepinephrine and epinephrine, is partially protein bound in serum, has a short half life (t₁/₂ = 1-2 minutes) and requires 5 to 30 minutes to reach a steady-state concentration. Even with weight-based dosing there are fluctuations in dopamine plasma level and the steady-state concentration varies widely in the critically ill population. Although classically taught, the weight-based dosing of dopamine is more didactic than practical: at doses lower than 5

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VSMC – vascular smooth muscle cells; EC – endothelial cells; NO – nitric oxide. α₁ (A, B, D) – alpha 1 adrenergic receptor subtypes A, B, D; α₂ (A, C) – alpha 2 adrenergic receptor, subtypes A, C; β₁, β₂, β₃ – beta adrenergic receptors 1, 2, 3; DA₁ and DA₂ – dopaminergic receptors A₁ and A₂; V₁, V₂, V₃ – vasopressin receptors.
µg/kg/min dopamine acts on DA₁ and DA₂ receptors in the renal, mesenteric, and coronary vascular beds causing vasodilation; at 5 to 10 µg/kg/min dopamine stimulates β₁ receptors enhancing heart rate and contractility; over 10 µg/kg/min dopamine activates α₁ receptors causing vasoconstriction and increased blood pressure. These effects overlap, especially in critically ill patients with the median dose required to restore blood pressure being 15µg/kg/min. Dopamine also inhibits aldosterone release and Na⁺/K⁺ ATPase promoting diuresis.3,24 The diuretic effect of dopamine was reported as early as 1963.27 Many studies have associated the diuretic effect of dopamine with the improvement of renal function since then.28 A large retrospective analysis conducted in the United States, however, revealed that the use of low-dose dopamine does not decrease the incidence of acute renal failure or the need for hemodialysis.29 Two meta-analyses published in early 2000 revealed similar results: neither prevention nor improvement of acute renal failure nor reduced mortality.30,31 A well designed, large prospective study conducted in Australia and New Zealand found that there is no difference in urine output at different time points with the use of renal-dose dopamine or placebo and no benefit of this treatment in acute renal failure.32 Moreover, low dose dopamine could even induce renal failure by redistribution of the renal flow out of the already compromised renal medulla.33

Dopamine increases oxygen delivery to the hepato-splanchnic circulation by 65% and oxygen consumption by 16%.2,24 Intramucosal pH (pHi) diminishes with the use of dopamine and various mechanisms are proposed in the literature: direct effect on gastric cells, decrease of mucosal flow or impairment of hepato-splanchnic metabolism.3,35,36 It is widely recognized that dopamine impedes the gastroduodenal motility3 which can affect enteral feeding.37,38

Dopamine has a plethora of endocrine and immunological effects: decreased the prolactin secretion and increased susceptibility to infections;prolonged infusion leading to suppressed growth hormone metabolism; dampened thyroid stimulating hormone as well as thyroxin and triiodothyronine and subsequently affected glucose and lipid metabolism.39-41 This “euthyroid sick syndrome” severity is proportional to the duration of dopamine infusion.42

Dopamine affects ventilatory drive by impeding the response to hypoxia and hypercapnia and patients appear paradoxically easier to wean from mechanical ventilation.43 Dopamine alters ventilation perfusion matching by augmenting the shunt effect.44 This vasoactive drug increases the risk of tachycardia and arrhythmia, oxygen demand and the propensity for myocardial ischemia.44,45

A prospective, multicenter, observational study of 110 patients with septic shock suggested that dopamine resistant septic shock predicts an increased risk of mortality.46 Another large, prospective, multicenter, observational study (included 3147 patients, 469 diagnosed with septic shock) showed an association of dopamine and epinephrine with higher mortality rates, but not of norepinephrine and dobutamine.47 This study revealed that in 2002 in Europe norepinephrine was the most widely used agent for shock (80%) followed by dopamine (35%).47 (Fig. 1)

![Figure 1. Frequency of vasoactive drug use in 1,058 patients with shock. Sepsis Occurrence in Acutely Ill Patients (SOAP) Study (DA - dopamine, DO - dobutamine, E - epinephrine; N - norepinephrine).47](image)

**VASOPRESSOR USE IN THE ICU: NOREPINEPHRINE**

Norepinephrine is an endogenous mediator and a potent alpha-adrenergic agonist with some degree of beta-adrenergic activity which augments cardiac output by 10-20% and stroke volume by 10-15%.48 The mean dose reported in literature ranges between 0.2-1.3 µg/kg/min, but may be as low as 0.01 µg/kg/min or as high as 5.0 µg/kg/min in clinical practice. Large dose requirements could be related to the down-regulation of alpha receptors.49 Norepinephrine produces little or no effect on pulmonary pressure and has a good cardiovascular profile with maintenance of coronary perfusion and lack of marked chronotropic activity.2,50,51

A prospective, randomized, double-blinded trial showed that norepinephrine effectively restored hemodynamic abnormalities in 93% of the patients with septic shock while dopamine reversed the hemodynamic changes in 31 % of the patients.50 Norepinephrine combined with dobutamine
stimulates hepato-splanchnic flow.\textsuperscript{52, 53} Norepinephrine exerts a better influence on hepatic energy balance and metabolism of lactate than dopamine.\textsuperscript{54} Norepinephrine has no effect on moderate levels of lactate in septic shock, but it decreases high serum lactate levels.\textsuperscript{55} Various studies suggest that norepinephrine use enhances urine output, creatinine clearance and diminishes free water balance, serum creatinine and BUN in septic shock patients.\textsuperscript{3} During hemorrhagic and hypovolemic shock, the effect of norepinephrine on renal function is detrimental.\textsuperscript{53}

In a prospective, observational study, norepinephrine treatment was a positive predictive factor for survival by multivariate analysis.\textsuperscript{56} Two other prospective studies revealed that norepinephrine improves cerebral perfusion in traumatic brain injury compared to dopamine.\textsuperscript{57, 58} The Sepsis Occurrence in Acutely Ill Patients (SOAP) group is currently conducting a prospective randomized multicenter phase IV trial to compare dopamine with norepinephrine use in shock for various outcomes: 28 day survival, intensive care survival, hospital survival, severity of organ dysfunction in ICU (SOFA score), time spent on vasopressors, on renal replacement, mechanical ventilation and the occurrence of adverse events.\textsuperscript{59}

**VASOPRESSOR USE IN THE ICU: EPINEPHRINE**

Epinephrine is an alpha and beta adrenergic agonist, synthesized, stored and released by the chromaffin cells of the adrenal medulla. Epinephrine doses range from 1 to 10 µg/min. At a low dose epinephrine exerts mainly a beta effect, but as doses increase over 0.15-0.3 µg/kg/min it activates alpha receptors. Epinephrine increases: heart rate, cardiac output, stroke volume, oxygen delivery and consumption without affecting pulmonary capillary wedge pressure or pulmonary artery pressure.\textsuperscript{50, 61} At low doses epinephrine causes vasodilation in the calf vascular bed and diminishes diastolic blood pressure.\textsuperscript{61} At high dose it enhances systemic vascular resistance and diastolic blood pressure.\textsuperscript{62} Epinephrine exerts a good hemodynamic profile in patients with right ventricular insufficiency and promotes contractility.\textsuperscript{53}

Epinephrine increases glucose and serum lactate level, causes lipolysis and leukocytosis, and exerts an anticoagulant effect.\textsuperscript{50, 64, 65} In 2003, Levy hypothesized that the lactate level rises with epinephrine infusion due to aerobic glycolysis and stimulation of muscle Na+/K+-ATP-ase and the Cori cycle.\textsuperscript{66} Arterial, splanchnic and hepatic venous lactate concentrations may be transiently increased.\textsuperscript{56, 67}

Various studies unveiled that epinephrine infusion increased pH, P\textsubscript{CO\textsubscript{2}} gap, but no benefit on survival was found by normalizing these parameters.\textsuperscript{3} Two trials recently revealed that epinephrine is superior to norepinephrine combined with dobutamine in promoting gastric mucosal flow.\textsuperscript{68, 69} Other data published suggested that epinephrine use impedes oxygen extraction.\textsuperscript{51, 67} An experimental hemodynamic septic shock model revealed that epinephrine significantly reduces renal flow.\textsuperscript{70} Martin and colleagues observed that epinephrine is added as a vasopressor in clinical practice if norepinephrine fails to restore the blood pressure at a dose of 5 µg/kg/min.\textsuperscript{56} Epinephrine is not recommended as a first line vasopressor treatment for septic or cardiogenic shock.\textsuperscript{50, 71} The results of a phase IV large trial comparing epinephrine alone versus a combination of norepinephrine with dobutamine showed no difference in outcomes in septic shock mortality, time to hemodynamic stability, vasopressin free days.\textsuperscript{72}

**VASOPRESSOR USE IN THE ICU: PHENYLEPHRINE**

The recommended dose of phenylephrine, a selective \(\alpha\)-agonist, is 0.5-8 µg/kg/min. Initially used to treat supraventricular tachycardia due to its heart rate slowing effect by vagal reflex, phenylephrine mainly affects mean arterial pressure, systemic vascular resistance and stroke volume. The impact on cardiac output and cardiac index was reported differently in various studies: a retrospective analysis found that heart rate is not perturbed by phenylephrine administration while cardiac index was described to be either constant or enhanced.\textsuperscript{53, 73-75}

**VASOPRESSOR USE IN THE ICU: VASOPRESSIN**

Vasopressin, also known as antidiuretic hormone, is synthesized by the hypothalamus, stored in the posterior lobe of the pituitary gland and acts on three types of receptors (\(V_\text{1}\), \(V_\text{2}\), and \(V_\text{3}\)). Originally approved to treat diabetes insipidus, vasopressin recently entered into the armamentarium of shock treatment.\textsuperscript{76} Although initially used at high doses and titrated to blood pressure, vasopressin now tends towards lower and fixed dosages with the current recommendation being 0.01-0.04 UI/min.\textsuperscript{10, 22} Vasopressin exerts numerous effects: blood osmolality and volume maintenance acting on kidney, control
of blood pressure by vasoconstriction, modulation of corticotropin (ACTH) release, enhancement of thrombocyte formation and aggregation, memory and social behavior influence.\textsuperscript{77-79} $V_1$ receptors are responsible for vasoconstriction in most vascular beds while $V_2$ receptors mediate the antidiuretic effects on the distal convoluted tubule and the collecting ducts and $V_3$ receptors stimulate corticotropin secretion in the anterior hypophysis.\textsuperscript{22}

Hypotension and shock increase vasopressin release, and high serum levels are seen after cardiac arrest, hemorrhage, epidural anesthesia, septic shock or exercise.\textsuperscript{80} In septic shock, serum vasopressin values decline over 96 hours to physiologic, but inappropriate low levels.\textsuperscript{81, 82} A recent study revealed that vasopressin levels at 24 hours were significantly related to male sex, alone in less severe septic shock.\textsuperscript{91} that vasopressin might be superior to norepinephrine versus Norepinephrine in Septic Shock”) a multicenter, triple-blinded, randomized, controlled study revealed.

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Terlipressin, a synthetic analog of vasopressin with a longer duration of action ($t_{1/2} = 6$ hrs), is administered in bolus (1 mg) doses. Terlipressin diminishes platelet count and increases transaminase and bilirubin levels.\textsuperscript{92} Rebound hypotension can occur with treatment discontinuation.\textsuperscript{93} Two studies stated that terlipressin augments mean arterial pressure, urine output and creatinine clearance, and promotes gastric mucosal perfusion, while reducing cardiac output and heart rate.\textsuperscript{94,95}

\textbf{INOTROPE USE IN THE ICU: DOBUTAMINE} 

Dobutamine is a racemic mixture of a dextro-isomer exerting the $\beta_1$-adrenergic activity and a levo-isomer responsible for the $\alpha_1$-adrenergic effects.\textsuperscript{3, 96} The doses range between 2 and 28 $\mu$g/kg/min with patients receiving concomitant $\beta$-blocker requiring higher dosages. Dobutamine has more of an inotropic than a chronotropic effect, but the cumulative cardiac outcome varies widely between studies: increase in cardiac index (12-61\%), stroke volume (23-58\%) and heart rate (9-23\%).\textsuperscript{97} Dobutamine increases heart rhythm especially in patients with low filling pressure or diagnosed atrial fibrillation.\textsuperscript{97}

Dobutamine’s effects on the peripheral vasculature is weak (oppose $\alpha_1$ vasoconstriction with $\beta_1$ vasodilation) and at a low dose it may exert a mild vasodilator effect.\textsuperscript{96,97} In hypotensive circumstances dobutamine is often administered with vasopressors to restore kidney and gut blood flow.\textsuperscript{97} De Backer recently suggested that dobutamine infusion improves sublingual capillary perfusion in patients with septic shock proportional to the lactate level decrease.\textsuperscript{98} Dobutamine infusion is currently recommended for decompensated cardiac heart failure when prognosis and clinical course are critically dependent on hemodynamics and for septic shock if volume repletion, vasopressors and transfusion up to 30\% hematocrit do not restore $SeVO_2 > 70\%$.\textsuperscript{10,96}

\textbf{INOTROPE USE IN THE ICU: PHOSPHODIESTERASE INHIBITORS (PDEIs)} 

Amrinone, milrinone, and enoximone inhibit degradation of cyclic adenosine monophosphate (cAMP) by phosphodiesterases, subsequently enhancing intracellular calcium. These drugs promote myocardial contractility and systemic vasodilation and determine a potent pulmonary vascular dilatation.\textsuperscript{36,99,100} PDEIs appear to be useful in patients with residual $\beta$-blockade or $\beta$-receptor down-regulation.\textsuperscript{99} Several open label studies suggest a favorable hemodynamic
effect of PDEIs when combined with β-adrenergic agonists. A large prospective, randomized, controlled trial of patients with acute systolic heart failure (OPTIME CHF) revealed more adverse events with no difference in survival with the use milrinone compared to placebo.

INOTROPE USE IN THE ICU: LEVOSIMEDAN

Levosimeden causes Ca++ sensitization of troponin C and opens the KATP channel in myocytes and smooth muscle cells stimulating heart contractility and diminishing vascular resistance without increasing oxygen requirements. Levosimeden has an active metabolite with a long half-life and it is administered as a loading dose of 12 µg/kg over 10 minutes followed by 0.1-0.2 µg/kg/min for up to 24 hrs infusion. Levosimeden's hemodynamic effect declines slowly over a week following a 24 hours infusion due to its long acting metabolite.

In patients with severe heart failure (LIDO study), levsimeden augmented cardiac output, diminished pulmonary capillary wedge pressure and pulmonary pressure and improved survival up to 180 days compared to placebo. Recent small, controlled studies found that levsimeden compared to placebo decreases pulmonary pressure in patients with acute respiratory distress syndrome, has a good cardiovascular profile and reduces lactate level in septic shock. The Randomized Multicenter Evaluation of Intravenous Levosimedan Efficacy Versus Placebo (REVIVE II) study revealed favorable outcomes with the use of levsimeden vis-à-vis placebo in patients with worsening congestive cardiac failure and dyspnea at rest requiring intravenous diuretics. Levsimeden compared to dobutamine showed no difference in long term survival in patients with acute heart failure in need of intravenous inotropic support (SURVIVE trial).

CONCLUSIONS AND NEW TRENDS

Several trends are obvious in reviewing the use of vasopressors and inotropes in the treatment of shock over the last decade. The use of dopamine has dramatically changed and the concept of improving morbidity by preferentially increasing blood flow to the kidney with this agent is largely discredited. Early goal directed therapy in septic shock patients has focused our attention on the importance of volume resuscitation prior to the application of vasopressors. The use of inotropes and chronotropes with pressure restoration has been tempered and our goals for oxygen delivery have been sharpened. While the importance of rapid resuscitation is clearer, we now recognize that attempts to improve oxygen delivery to supra-physiologic levels have minimal positive effects. The use of markers of perfusion such as lactate level and ScVO₂ or StO₂ is on the rise along with our recognition of what an appropriate blood pressure goal might be for patients with shock. Through large network efforts, such as the SOAP group, we now know what constitutes common patterns of use for vasopressors and inotropes. We can also see where national usage patterns vary and how adoption of new practice patterns, such as vasopressin use, may be limited.

Clinicians caring for the critically ill are demanding better evidence for their use of drugs. In shock, the trials currently being conducted with vasopressors are large enough to answer questions of mortality and morbidity instead of effect on the secondary markers of blood pressure and cardiac output. The limitations of extrapolating data from single site reports to larger populations is better recognized and even results with strong mortality improvements, such as early goal directed therapy in septic shock, are being subjected to confirmation by multi-center trials. The use of invasive monitoring with right heart catheterization is under strong scrutiny for both its value and risk while advances in bioengineering are making the dream of deriving the same information non-invasively closer to reality.

There are many questions about the use of vasopressors and inotropes in shock that remain unanswered. Is there a way to predict which agent an individual patient will respond to with a superior cardiodynamic profile and limited risk of adverse events? Do lower dose combination therapies result in better mortality outcomes than higher dose single agents? Do the previous answers change with duration of therapy? Are there genomic markers that are important in the treatment response? Does our ability to achieve current treatment goals actually affect overall outcome and is there a time-dependency to this response? Our most popular treatments for shock are over 25 years old and these basic questions still remain. Our capability to capture, analyze and share the results of treatment decisions regarding shock is increasing with better computer systems in the intensive care units. Hopefully, over the next decade, we will continue to see trends that move our use of vasopressors and inotropes closer to the science than the art of medicine.
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