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Review Article

Vasopressors and Inotropes in Shock: Which One to Choose?

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Abstract: Hemodynamic shock is a final common pathway associated with regularly encountered emergencies including myocardial infarction, microbial sepsis, pulmonary embolism, significant trauma and anaphylaxis. Shock results in impaired tissue perfusion, cellular hypoxia, and metabolic derangements that cause cellular injury. Prompt recognition and intervention are the cornerstones of mitigating the dire consequences of shock. The maintenance of end-organ perfusion is critical to prevent irreversible organ injury and failure, and this frequently requires the use of fluid resuscitation and vasopressors and/or inotropes. Despite the widespread use of different vasopressors and inotropes in various types of shock, the understanding of their clinical effects is often inadequate and therefore, leads to erroneous therapeutic decision making. This article focusses on reviewing the underlying mechanisms of action of commonly employed vasopressors and inotropes, analysing published data on their clinical application in various types of shock, and finally, choosing the right vasopressor(s) and/or inotrope(s) in the management of various shock syndromes.
Keywords: Shock, Vasopressors, Inotropes, Cellular hypoxia.

INTRODUCTION

Hemodynamic shock or circulatory shock is classically described as a life-threatening acute clinical syndrome of inadequate blood perfusion to the tissues resulting in cellular injury and severe tissue dysfunction [1]. Although this early injury is often reversible, persistent hypoperfusion leads to irreversible tissue damage, progressive organ dysfunction, and can progress to death [2]. Prompt recognition and intervention are the cornerstones of mitigating the dire consequences of shock. Unlike other types of clinical syndromes (e.g., chest pain), for which a clinical diagnosis is made before treatment is initiated in earnest, the treatment of shock often occurs concurrently or ahead of the diagnostic process. The maintenance of end-organ perfusion is critical to prevent irreversible organ injury and failure, and this frequently requires the use of fluid resuscitation and vasopressors and/or inotropes. Inotropes are agents which can increase myocardial contractility and therefore cardiac output (CO) whereas vasopressor agents increase vascular tone and thereby elevate mean arterial pressure (MAP).

The clinical manifestations and prognosis of shock are largely dependent on the etiology and duration of insult. The most widely accepted classification system (Weil and Shubin classification system) [3] organizes shock into four broad categories: (1) Hypovolemic, (2) Cardiogenic, (3) Obstructive, and (4) Distributive. Patients who are in shock often have overlap between these categories, but determining which form of shock is primarily involved, is helpful for further definitive management.

INITIAL THERAPY AND DIAGNOSTIC APPROACH

As mentioned previously, once shock is recognized, certain immediate steps should be undertaken while the cause of shock is determined:

- If the patient's airway, oxygenation, or ventilation is not effective, then the patient should be intubated.
- Large-bore intravenous access should be established.
- Any arrhythmias should be addressed as per the standard advanced cardiac life support protocols.
- A trial of at least 1.0 L of crystalloid should be infused to treat hypotension; the fear of pulmonary edema should not preclude the use of volume in a patient who is not perfusing adequately. In cardiogenic shock, this fluid challenge will not be as harmful as compared to sustained hypotension [4].
- Vasopressors should only be initiated with/after adequate resuscitation is provided with crystalloids, colloids, and/or blood products. Vasopressors are not recommended in the initial stabilization of hemorrhagic shock [5]. Permissive hypotension may be employed

until bleeding is controlled in patients requiring emergent surgical intervention [6]. In low cardiac output states, the use of an inotropic agent should be considered.

- The diagnosis of acute myocardial infarction (AMI), tension pneumothorax, cardiac tamponade, and massive pulmonary embolism should be considered on the basis of the available information. If any of these diagnoses is being considered, then targeted diagnostic and therapeutic interventions should proceed while more formal diagnostic investigations occur concurrently.

Once the patient is stabilized, the cause of shock can be safely assessed. In certain instances, the clinical situation may point to an obvious cause, in which case the treatment should be initiated for that cause of shock (e.g., antibiotics for septic shock); however, given the myriad causes of shock, a structured diagnostic approach should still be conducted because of the ability of certain types of shock to masquerade as one another and for multiple types of shock to coexist. The key to distinguish distributive shock from other categories of shock is an objective assessment of cardiac function. An echocardiogram, a pulmonary artery catheter, or an indwelling arterial line cardiac output assessment should be conducted as soon as possible. This cardiac assessment should occur while other targeted diagnostic investigations are ongoing. To summarise, the next steps for the diagnostic work-up for a patient who is in shock should be as follows [4]:

- Complete blood count, complete serum biochemistry, serum lactate, arterial blood gas analysis, cardiac enzymes, electrocardiogram, chest radiograph, random serum cortisol, and coagulation assessment.
- Echocardiogram, pulmonary artery catheter, or an indwelling arterial line CO measurement.

On the basis of the results of these investigations, the cause of shock can be ascertained. In general, in hypovolemic and distributive shock, the patient is volume responsive. Volume responsive means that as volume is infused, the cardiac index (CI) increases significantly. In case of hypovolemic shock, if the volume is replaced faster than the volume being lost, then both blood pressure (BP) and CI will increase proportionately. In patients with distributive shock, the CI will respond significantly to volume, but the BP will often remain low as the hyperdynamic state evolves. Usually, the CI will increase to a zenith, at which point volume no longer improves the CI yet the patient remains hypotensive, requiring the use of vasopressors. If the patient's CI is less than 2.0 despite volume resuscitation, then obstructive or cardiogenic shock must be considered [4].

Table 1: Showing various types of shock and their common causes

Types of Shock	Common Causes
1. Hypovolemic	Hemorrhage, vomiting, diarrhoea, burns, polyuria (diabetic ketoacidosis), capillary leak causing "third spacing"
2. Cardiogenic	Myocardial infarction, cardiomyopathy, drugs (e.g. overdose of beta blockers), valvular diseases, arrhythmias, myocarditis
3. Obstructive	Tension pneumothorax, pulmonary embolism, air embolism, cardiac tamponade, aortic dissection
4. Distributive	- SIRS (Systemic inflammatory response syndrome) related: Sepsis, pancreatitis, trauma, burns - Neurogenic: Spinal cord injury - Endocrine related: Adrenal insufficiency, thyrotoxicosis - Anaphylactic - Liver failure

BRIEF REVIEW OF COMMON VASOPRESSORS AND INOTROPES

Catecholamines

They can be endogenous (epinephrine, norepinephrine, dopamine) or synthetic (dobutamine, isoprenaline, phenylephrine). Cardiovascular effects of these agents are mediated through their interaction with adrenergic and dopaminergic receptors. The four major adrenergic receptors are α_1, α_2, β_1 and β_2 receptors. In the cardiovascular system, activation of the α_1 receptor induces vasoconstriction and increase in systemic vascular resistance (SVR) whereas activation of the α_2 receptor reduces norepinephrine release at the synaptic end plate, thus mildly decreasing blood pressure and being mildly negatively dromotropic. Activation of the β_1 receptor, conversely, increases CO by its positive chrono-, dromo-, and inotropic actions, whereas activation of the β_2 receptor results in vasodilation [7]. Dopaminergic receptors (D1 and D2) are concentrated in the kidney and splanchnic vasculature, and stimulation of these leads to renal and mesenteric vasodilatation.

The density and proportion of these receptors are responsible for variations in the physiological responses of inotropes and vasopressors in individual tissues. Response of various vasopressor and inotropic agents is further modified by reflex autonomic changes after acute BP alterations and effect of hypoxia or acidosis on the binding affinities of these agents to adrenergic receptors [8].

Epinephrine

Epinephrine or Adrenaline is a potent mixed α and β adrenergic agonist. The β adrenergic effects are more pronounced at low doses and α adrenergic effects predominate at higher doses. Low dose of epinephrine increases CO because of β_1 receptor mediated inotropic and chronotropic effects, while α_1 receptor induced vasoconstriction is often counterbalanced by β_2 receptor mediated vasodilation [9]. The result is an increased CO with decreased SVR and a variable effect on MAP. However, at higher doses, α receptor mediated vasoconstriction predominates which results in increased SVR in addition to increased CO. High and prolonged doses can cause direct cardiac toxicity through damage to arterial walls, which causes focal regions of myocardial contraction band necrosis, and through direct stimulation of myocyte apoptosis [10]. Epinephrine can also cause tachyarrhythmia, lactic acidosis, and hyperglycemia [11]. Lactic acidosis and hyperglycemia are caused by epinephrine induced hypermetabolism, suppression of insulin release, and glycolysis. In addition, epinephrine can compromise hepatosplanchnic perfusion, oxygen exchange, and lactate clearance, especially in septic shock [12,13]. In animal models, these adverse effects are dosage related and more pronounced as compared with norepinephrine or vasopressin [12,13].

Epinephrine is the first-line catecholamine in cardiopulmonary resuscitation and anaphylactic shock. As a vasopressor and as an inotrope, it is usually considered a second-line agent.

Norepinephrine

Norepinephrine or noradrenaline has potent α_1 and modest β adrenergic effects which render it a powerful vasoconstrictor with less potent direct inotropic properties [14]. It has minimal chronotropic effects because of which it is a drug of choice in settings where heart rate stimulation is undesirable. Because of its marked vasoconstrictive characteristics, norepinephrine seems the logical drug of choice in distributive forms of shock by increasing MAP, effective circulating blood volume, and thus venous return and preload, with minimal increase of heart rate or stroke volume. It is more potent than dopamine and is commonly considered the first-choice vasopressor to reverse hypotension in vasodilatory shock [15]. Some clinicians fear that the use of norepinephrine will cause severe vasoconstriction in visceral and renal microvasculature, yet norepinephrine seems to improve parameters of visceral microperfusion when hypotension is reversed in septic shock, compared with epinephrine or dopamine [16,17]. This may explain why norepinephrine therapy is associated with some survival benefit in septic shock, compared with high-dosage dopamine or epinephrine [18]. In comparison with epinephrine, norepinephrine demonstrates many fewer metabolic adverse effects. Coronary flow is increased owing to elevated diastolic blood pressure and indirect stimulation of cardiomyocytes, which release local vasodilators [19]. Prolonged norepinephrine infusion can have a direct toxic effect on cardiac myocytes by inducing apoptosis via protein kinase A activation and increased cytosolic Ca^{2+} influx [20].

Dopamine

Dopamine is an α and β adrenergic agonist that also stimulates dopaminergic receptors D_1 and D_2. The effects of dopamine are dose-dependent. At low doses (1-3 μg/kg/min), it acts predominantly on D_1 receptors in the renal, mesenteric, cerebral and coronary vessels resulting in selective vasodilation. It is postulated that dopamine increases urine output by augmenting renal blood flow and glomerular filtration rate [21], however, the clinical significance of "renal-dose" dopamine is controversial because a renal protective effect has not been conclusively demonstrated [21]. At intermediate doses (3-10 μg/kg/min), β_1 adrenergic effect of dopamine predominates and results in increase in CO, with variable effect on heart rate. At higher doses (10-20 μg/kg/min), α_1 adrenergic effect of dopamine predominates and results in vasoconstriction which leads to an increase in SVR and MAP [7]. The α and β adrenergic effects of dopamine are generally weaker compared with epinephrine or norepinephrine. Dopamine is used as a vasoconstrictor in vasodilatory shock and as an inotrope in low CO states. Dopamine's niche indication is vasodilatory shock associated with bradycardia, both of which can be corrected with this agent. Despite the theoretical beneficial effect of dopamine on splanchnic perfusion by stimulation of D1 receptors, this has not been reproduced in critically ill patients. Published data in sepsis suggest that dopamine may impair hepatosplanchnic perfusion and metabolism [22,23,24]. Tachycardia, another adverse effect of dopamine, together with vasoconstriction can lead to increased cardiac oxygen demand and decreased oxygen delivery and may trigger myocardial ischemia and arrhythmias [24].

Dobutamine

Dobutamine is a synthetic catecholamine with predominant β adrenergic and only limited α adrenergic effects. As a result of β_1 receptor mediated positive inotropic, and β_2 receptor mediated vasodilatory action, dobutamine increases CO and decreases systemic and pulmonary vascular resistance. Dobutamine is the preferred vasoactive agent to treat cardiogenic shock with low output and increased afterload. In combination with norepinephrine, dobutamine is used in septic shock

with myocardial dysfunction. α_1 receptor mediated vasoconstriction progressively dominates at higher dosages [25]. Despite its mild chronotropic effects at low to medium doses, dobutamine significantly increases myocardial oxygen consumption [26]. This may limit its utility in clinical conditions in which induction of ischemia is potentially harmful. Tolerance can develop after just a few days of therapy [27], and malignant ventricular arrhythmias can be observed at any dose.

Table 2: Commonly used Vasopressor and Inotropic Drugs - Indication, Dose, Receptor binding, Side effects

	Adrenaline	**Noradrenaline**	**Dopamine**	**Dobutamine**
Clinical Indication	Cardiogenic, Septic, Anaphylactic shock, Cardiac arrest	Septic, Cardiogenic, Vasodilatory shock	Cardiogenic, Septic shock	Low CO (Cardiogenic shock, Sepsis induced myocardial dysfunction)
Dose	Infusion: 0.01-0.1 µg/kg/min, Bolus: 1 mg IV every 3-5 min (max: 0.2 mg/Kg), IM: (1:1000): 0.1-0.5 mg (max 1 mg)	0.01-3 µg/kg/min	2-20 µg/kg/min	2-20 µg/kg/min
Receptor binding				
α_1	+++++	+++++	+++	+
β_1	++++	+++	++++	+++++
β_2	+++	++	++	+++
DA	**N/A**	N/A	+++++	**N/A**
Major Side effects	Arrhythmias, Cardiac ischemia, Sudden cardiac death, Hypertension	Arrhythmias, Bradycardia, Digital ischemia, Hypertension	Arrhythmias, Cardiac ischemia, Hypertension, Tissue ischemia/gangr-ene	Tachycardia, arrhythmias, Cardiac ischemia

Phenylephrine

Phenylephrine is a potent α_1 adrenergic agonist with virtually no affinity for β adrenergic receptors. It is commonly used as a rapid bolus for immediate correction of sudden severe hypotension until more definitive therapies are instituted. It can be used to raise MAP in patients with severe hypotension and concomitant aortic stenosis, to correct hypotension caused by simultaneous ingestion of sildenafil and nitrates, to decrease the outflow tract gradient in patients with obstructive hypertrophic cardiomyopathy, and to correct vagally mediated hypotension during percutaneous diagnostic or therapeutic procedures. This agent has virtually no direct effect on heart rate; although it has the potential to induce significant baroreceptor mediated reflex rate responses after rapid alterations in MAP [7].

Vasopressin

Vasopressin or "antidiuretic hormone" exerts its circulatory effects through V_1 receptors on vascular smooth muscles and V_2 receptors on renal collecting duct system. V_1 receptor stimulation mediates vasoconstriction whereas V_2 receptor activation mediates water reabsorption by enhancing renal collecting duct permeability. Overall, vasopressin tends to cause increase in SVR. Vasopressin modulated increase in vascular sensitivity to noradrenaline further augments its vasopressor effect. Septic shock is associated with relative deficiency of vasopressin. Exogenous administration of vasopressin reverses vasodilation in vasopressor-resistant shock by activation of V_1 receptors, inhibition of ATP-sensitive potassium channels [28], attenuation of nitrous oxide production [29], and amplification of vasoconstrictive catecholamine effect [30]. Vasopressin is a second-line agent in septic shock or refractory hypotension that is unresponsive to norepinephrine (or epinephrine). Furthermore, the pressor effects of vasopressor are relatively preserved during hypoxic and acidotic conditions, which commonly develop during shock of any origin.

OPTIMAL SELECTION OF VASOPRESSORS AND INOTOPES IN VARIOUS TYPES OF SHOCK

Hemorrhagic Shock

Vasopressors are rarely indicated and should be considered only when volume replacement is complete, haemorrhage is arrested and hypotension continues [5]. Permissive hypotension is evolving as a treatment strategy in which the goal is to keep the blood pressure low enough to avoid exsanguination but maintain perfusion of end organs [6]. Early vasopressor use within the first 24 hours in patients not appropriately resuscitated with blood products and fluids has been suggested to increase the risk of mortality [31].

Cardiogenic Shock

Inotropes and vasopressors, when used in the setting of cardiogenic shock complicating AMI, can increase myocardial oxygen consumption and can cause ventricular arrhythmias, contraction-band necrosis, and infarct expansion. However, critical hypotension itself compromises myocardial perfusion, leading to elevated left ventricular (LV) filling pressures, increased myocardial oxygen requirements, and further reduction in the coronary perfusion gradient. Thus, hemodynamic benefits usually outweigh specific risks of inotropic therapy when used as a bridge to more definitive treatment measures. The lowest possible doses of inotropic and pressor agents should be used to adequately support vital tissue perfusion while limiting adverse consequences. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for ST-elevation myocardial infarction (STEMI) recommend the selection of vasopressor and/or inotrope therapy based on systolic blood pressure (SBP) plus the presence or absence of signs and symptoms of shock [32]. For patients with a SBP of 70-100 mm Hg, dobutamine is recommended in the absence of shock and dopamine if shock is present. Norepinephrine is recommended when SBP is <70 mmHg. However, the results of a multicenter, randomized trial conducted in 2010 by De Backer et al challenged the recommendation of dopamine as a first line vasopressor agent over norepinephrine in cardiogenic shock patients. The trial was conducted to determine if the use of norepinephrine over dopamine as the first line vasopressor agent could reduce the rate of death among patients in shock [33]. Although no difference was found in the primary outcome of 28-day mortality, a subgroup analysis found a higher mortality rate in cardiogenic shock patients who received dopamine. The exact cause of this increased mortality could not be determined. Moderate doses of combination of medications may be more effective than maximal doses of any individual medication. Dobutamine may be initiated in combination with norepinephrine in cardiogenic shock and thus reduce the side effects associated with high doses of each drug.

Septic Shock

Septic shock results when infectious agents or infection-induced mediators in the bloodstream produce hemodynamic decompensation. Its pathogenesis involves a complex interaction among pathologic vasodilation, increased capillary permeability, relative and absolute hypovolemia, myocardial dysfunction, and altered blood flow distribution due to the inflammatory response to infection [34]. When fluid administration fails to restore an adequate arterial pressure and organ perfusion in patients with septic shock, therapy with vasopressor(s) with or without inotrope(s) should be initiated to achieve the desired physiological target. The use of vasopressor and inotropic agents in the lowest possible dose and for minimum period of time is most appropriate.

Numerous studies have been suggestive of some advantage of norepinephrine and dopamine over epinephrine [15,18]. Septic patients may have low, normal, or increased cardiac output. Therefore, treatment with a combined inotrope/vasopressor, such as noradrenaline or dopamine, is recommended if cardiac output is not measured. As per the Surviving Sepsis Campaign guidelines [35], norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in septic shock. A meta-analysis of dopamine versus norepinephrine in the treatment of septic shock also concluded that dopamine administration is associated with greater mortality and a higher incidence of arrhythmia events [36].

In hyperdynamic septic shock, during which urine flow is believed to decrease mainly because of lowered renal glomerular perfusion pressure, the use of norepinephrine markedly improves MAP and glomerular filtration. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance [37-40].

In 2008, the VAAST trial compared norepinephrine plus vasopressin to norepinephrine alone in the treatment of septic shock and found no difference in 28-day mortality rates or overall rates of serious adverse events [41]. Dobutamine may be initiated in combination with norepinephrine in patients with myocardial dysfunction (i.e. elevated cardiac filling pressure, low CO) alongwith septic shock [34].

The latest recommendations of Surviving Sepsis Campaign (revised in 2012) regarding use of vasopressor(s) and/or inotrope(s) in septic shock are as follows [42]:

- Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of vasopressors in patients with septic shock. When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not been resolved or when a fluid challenge is in progress.
- Apply Vasopressor(s) to maintain MAP ≥65 mm Hg.
- Norepinephrine is the first choice vasopressor agent to correct hypotension in septic shock.

- Epinephrine (added to and potentially substituted for norepinephrine) may be used when an additional agent is needed to maintain adequate BP.
- Vasopressin 0.03 units/minute can be added to norepinephrine with intent of either raising MAP or decreasing norepinephrine dosage.
- Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
- Dopamine may be used as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., a patient with low risk of tachyarrhythmias and absolute or relative bradycardia). Dopamine increases MAP primarily by increasing CI with minimal effects on SVR.
- Low-dose dopamine should not be used for renal protection.
- The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine with dopamine or dopamine alone. A trial of dobutamine infusion may be administered or added to vasopressor in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low CO, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
- Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and BP persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target.

Anaphylactic Shock

Adrenaline is the treatment of choice for anaphylaxis. The recommended dose is 0.3 to 0.5 mg (concentration of 1:1000) intramuscularly (IM) every 5 to 10 minutes for adults [43]. Intravenous epinephrine is reserved for cases of cardiovascular collapse or those who fail to respond to IM therapy [44].

Neurogenic Shock

Neurogenic shock most often occurs in patients with severe spinal cord injury at the cervical or high thoracic level [45]. A shock state occurs as a result of sympathetic denervation leading to reduced sympathetic outflow to the cardiovascular system and subsequent decreased CO and SVR [46]. Neurogenic shock can occur at any time, from initial presentation to several weeks post injury [46]. The primary treatment for neurogenic shock is fluid resuscitation. If there is inadequate response to fluid resuscitation, vasopressors with alpha and beta activity such as norepinephrine should be initiated to counter the loss of sympathetic tone and provide chronotropic cardiac support [45].

CONCLUSION

There are only a few studies that provide evidence for a particular vasopressor or inotropic strategy in the early management of shock. Most recommendations for vasoactive strategies are largely based on pharmacodynamic modeling, animal research, empirical experience, and limited human trials performed in a critical care environment. Despite these limitations, a basic knowledge of the available evidence and a better understanding of the actions, limitations and side effects of individual vasoactive agent can help guide a physician to tailor therapy to specific patient presentations.

The vasopressors or inotropes should be used in the minimum possible dose and should be kept in a supportive context to allow treatment of the underlying disorder. Smaller combined doses of inotropes and vasopressors may be advantageous over a single agent used at higher dose to avoid dose-related adverse effects.

Norepinephrine is considered the first-line vasopressor in vasodilatory shock especially septic shock, dobutamine the first-line inotrope in shock associated with decreased cardiac output, and their combination in vasodilatory shock with decreased cardiac output. In cardiogenic shock complicating AMI, current guidelines based on expert opinion recommend dobutamine as the first-line agent for moderate hypotension (systolic blood pressure 70 to 100 mm Hg) and norepinephrine as the preferred therapy for severe hypotension (systolic blood pressure $<$70 mm Hg). Epinephrine is the first-line catecholamine in cardiopulmonary resuscitation and anaphylactic shock, and can also be used as a second line agent in shock that is unresponsive to other catecholamines. Vasopressin is emerging as a therapy in resistant vasodilatory shock. The use of other catecholamines and modern nonadrenergic vasoactive drugs in shock remains with little evidence. In general, results of large, high-quality trials of catecholamines and vasoactive agents for shock are urgently required to provide data for evidence-based guidelines for their use.

REFERENCES

1. Jimenez E; Shock. In Civetta JM, Taylor RW, Kirby RR editors; Critical Care, 3rd edition, Lippincott Williams & Wilkins, Philadelphia, 1997: 359-387.
2. Mitchell RN; Shock. In Kumar V editor; Robins and Cotran: Pathologic Basis of

Disease 6th edition, Saunders, Philadelphia, 2005: 134-138.
3. Weil MH, Shubin H; Proposed reclassification of shock states with special reference to distributive effects. In Hinshaw LB, Cox BG editors; The Fundamental Mechanisms of Shock. 1st edition, Plenum Press, New York, 1972: 13-23.
4. Rosenthal SF, Saner F, Chawla LS; Approach to hemodynamic shock and vasopressors. Clin J Am Soc Nephrol., 2008; 3(2): 546-53.
5. Martel MJ, MacKinnon KJ, Arsenault MY, Bartellas E, Klein MC; Hemorrhagic shock. J Obstet Gynaecol Can., 2002; 24(6): 504-520.
6. Duchesne JC, McSwain NE, Cotton BA; Damage control resuscitation: The new face of damage control. J Trauma, 2006; 69(4): 976-990.
7. Tabaee A, Givertz MM; Pharmacologic management of the hypotensive patient. In Irwin RS, Rippe JM editors; Irwin and Rippe's Intensive Care Medicine. 5th edition, Lippincott Williams & Wilkins, Philadelphia, 2003: 295-302.
8. Overgaard CB, Dzavík V; Inotropes and vasopressors: Review of physiology and clinical use in cardiovascular disease. Circulation, 2008; 118: 1047-1056.
9. Jones CJ, DeFily DV, Patterson JL, Chilian WM; Endothelium-dependent relaxation competes with α1- and α2-adrenergic constriction in the canine epicardial coronary microcirculation. Circulation, 1993; 87: 1264-1274.
10. Singh K, Xiao L, Remondino A, Sawyer DB, Colucci WS; Adrenergic regulation of cardiac myocyte apoptosis. J Cell Physiol, 2001; 189(3): 257-265.
11. Trager K, DeBacker D, Radermacher P; Metabolic alterations in sepsis and vasoactive drug-related metabolic effects. Curr Opin Crit Care, 2003; 9(4): 271-278.
12. De Backer D, Creteur J, Silva E, Vincent JL; Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? Crit Care Med., 2003; 31(6): 1659-1667.
13. Meier AH, Reinhart K, Bredle DL, Specht M, Spies CD, Hannemann L; Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med., 1997; 25(3): 399-404.
14. Bangash MN, Kong ML, Pearse RM; Use of inotropes and vasopressor agents in critically ill patients. Br J Pharmacol., 2012; 165(7): 2015-2033.
15. Martin C, Papazian L, Perrin G, Saux P, Gouin F; Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest, 1993; 103(6): 1826-1831.
16. Ledoux D, Astiz ME, Carpati CM, Rackow EC; Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med., 2000; 28(8): 2729-2732.
17. Marik PE, Mohedin M; The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. JAMA, 1994; 272(17): 1354-1357.
18. Martin C, Viviand X, Leone M, Thirion X; Effect of norepinephrine on the outcome of septic shock. Crit Care Med., 2000; 28(8): 2758-2765.
19. Tune JD, Richmond KN, Gorman MW, Feigl EO; Control of coronary blood flow during exercise. Exp Biol Med (Maywood), 2002; 227(4): 238-250.
20. Communal C, Singh K, Pimentel DR, Colucci WS; Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the α-adrenergic pathway. Circulation, 1998; 98: 1329-34.
21. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J; Low dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial - Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet, 2000; 356(9248): 2139-2143.
22. Guerin JP, Levraut J, Samat LC, Leverve X, Grimaud D, Ichai C; Effects of dopamine and norepinephrine on systemic and hepatosplanchnic hemodynamics, oxygen exchange, and energy balance in vasoplegic septic patients. Shock, 2005; 23(1): 18-24.
23. Martin C, Viviand X, Leone M, Thirion X; Effect of norepinephrine on the outcome of septic shock. Crit Care Med., 2000; 28(8): 2758-2765.
24. Debaveye YA, Van den Berghe GH; Is there still a place for dopamine in the modern intensive care unit? Anesth Analg, 2004; 98(2): 461-468.
25. Ruffolo RR; The pharmacology of dobutamine. Am J Med Sci., 1987; 294(4): 244-248.
26. Patel RN, Arteaga RB, Mandawat MK, Thornton JW, Robinson VJ; Pharmacologic stress myocardial perfusion imaging. South Med J., 2007; 100(10): 1006-1014.
27. Unverferth DA, Blanford M, Kates RE, Leier CV; Tolerance to dobutamine after a 72 hour continuous infusion. Am J Med., 1980; 69(2): 262-266.
28. Salzman AL, Vromen A, Denenberg A, Szabo C; K^+ (ATP)-channel inhibition improves hemodynamics and cellular energetics in hemorrhagic shock. Am J Physiol., 1997; 272(2 Pt 2): H688-694.

29. Kusano E, Tian S, Umino T, Tetsuka T, Ando Y, Asano Y; Arginine vasopressin inhibits interleukin-1 beta-stimulated nitric oxide and cyclic guanosine monophosphate production via the V1 receptor in cultured rat vascular smooth muscle cells. J Hypertens., 1997; 15(6): 627-632.
30. Hamu Y, Kanmura Y, Tsuneyoshi I, Yoshimura N; The effects of vasopressin on endotoxin-induced attenuation of contractile responses in human gastroepiploic arteries in vitro. Anesth Analg, 1999; 88(3): 542-548.
31. Sperry JL, Minei JP, Frankel HL; Early Use of Vasopressors after injury: Caution before constriction. J Trauma, 2008; 64(1): 9-14.
32. Antman EM, Anbe DT, Armstrong PW; ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation, 2004; 110(9): 282-92.
33. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D; Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med., 2010; 362: 779-89.
34. Dellinger RP; Cardiovascular management of septic shock. Crit Care Med., 2003; 31(3): 946-955.
35. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R *et al.*; Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med, 2008; 36(1): 296-327.
36. De Backer D, Aldecoa C, Njimi H, Vincent JL; Dopamine versus norepinephrine in the treatment of septic shock: a meta-analysis. Crit Care Med, 2012; 40(3): 725-730.
37. Redl-Wenzl EM, Armbruster C, Edelmann G; The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. Intensive Care Medicine, 1993; 19(3): 151-154.
38. Fukuoka T, Nishimura M, Imanaka H; Effects of norepinephrine on renal function in septic patients with normal and elevated serum lactate levels. Critical Care Medicine, 1989; 17(11): 1104-1107.
39. Martin C, Eon B, Saux P; Renal effects of norepinephrine used to treat septic shock patients. Critical Care Medicine, 1990; 18(3): 282-285.
40. Desjars P, Pinaud M, Bugnon D; Norepinephrine therapy has no deleterious renal effects in human septic shock. Crit Care Med., 1989; 17(5): 426-429.
41. Russell JA, Walley KR, Singer J; Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med, 2008; 358(9): 877-87.
42. Dellinger RP, Levy MM, Rhodes A; Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med, 2013; 41: 580-637.
43. Tupper J, Visser S; Anaphylaxis: A review and update. Can Fam Physician, 2010; 56(10): 1009-1011.
44. Sampson H, Munoz AF, Campbell RL, Adkinson NF, Bock SA, Branum A *et al.*; Second symposium on the definition and management of anaphylaxis: summary report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol., 2006; 117(2): 391-397.
45. Furlan JC, Fehlings MG; Cardiovascular complications after acute spinal cord injury: Pathophysiology, diagnosis, and management. Neurosurg Focus, 2008; 25(5): E13.
46. McMahon D, Tutt M, Cook AM; Pharmacological management of hemodynamic complications following spinal cord injury. Orthopedics, 2009; 32(5): 331.