

## The benefits and risks of vasoactive agents

Von Rahden RP, BSc(LabMed), MBBCh, DA(SA), FCA(SA), CertificateCriticalCare(Anaes)(SA)

Head, Clinical Unit; Department of Anaesthesia, Grey's Hospital, Pietermaritzburg; Clinical Lecturer, University of KwaZulu-Natal

Correspondence to: Richard von Rahden, e-mail: richard.vonrahden@kznhealth.gov.za; vonrahdenrp@yahoo.co.uk

Keywords: benefits, risks, shock, inotropes, vasopressors

### Abstract

Current shock resuscitation strategies require titration of fluid in combination with inotropes and vasopressors to counteract the actual pattern of circulatory abnormality in the patient, and to restore the circulation to a level that is adequate to prevent organ ischaemia. Used incorrectly or in excessive doses, vasoactive agents may cause patient harm. The mechanisms of shock, appropriate resuscitation goals, and some aspects of how common available vasoactive agents in South Africa can be used for optimal safety to help to achieve these goals are discussed.

© SASA

South Afr J Anaesth Analg 2014;20(1):40-42

### Introduction

Optimally managing circulatory shock regularly challenges anaesthesiologists tasked with stabilising patients for emergency procedures. "Shock" exists when the cardiovascular system cannot deliver enough oxygen to organs to meet their metabolic needs, resulting in organ damage and failure. Disorders of the microcirculation (arterioles and capillary beds) are contributors to shock states, but therapies to manipulate microcirculation are still developing. Therefore, this article focuses on current shock management strategies which involve manipulation of the heart, arteries and veins, using available agents in South Africa.

The circulation can be simplistically modelled as a hydraulic system of pipes (the arteries and veins) through which fluid (blood) is circulated by a pump (the heart).

Using this model, shock states can arise from four mechanisms:

- *Too little fluid within the system of pipes*: Hypovolaemic shock.
- *Pump failure*: Cardiogenic shock.
- *An abnormal increase in the size (dilation) of the pipes*: Distributive shock.
- *Blockage (intravascular obstruction or extravascular compression)*: Obstructive shock.

Therapies must address the shock mechanism or combination of mechanisms present in the patient at the

time. Obstructive shock needs directed therapy to relieve the obstruction. Pure hypovolaemic shock, such as that from recent haemorrhage, requires only the purposeful early replacement of fluid to refill the intravascular volume. Management of cardiogenic shock or distributive shock necessitates the administration of inotropes or vasopressors, respectively, in addition to judicious fluid administration. Most shocked patients in anaesthetic practice have multiple co-existing shock mechanisms.

Dysregulated hyperactivation of the innate immune system, the systemic inflammatory response syndrome, whether driven by infection ("septic shock") or by tissue injury or surgery, simultaneously promotes:

- Absolute hypovolaemia, i.e. fluid leaks from vessels into tissues due to endothelium-glycocalyx damage.
- Relative hypovolaemia, i.e. blood pools in dilated veins, especially splanchnic veins.
- Low arterial pressure due to arteriodilation.
- Some cardiac dysfunction, even though cardiac output may initially be supranormal.

All of these are aggravated by anaesthetic agents. Thus, multimodal therapy is required.

### Mechanisms of action of vasopressors and inotropes

Calcium ( $\text{Ca}^{2+}$ ) ions are the final regulators of muscle contraction in all muscle types, hence all vasoactive

agents, except the  $\text{Ca}^{2+}$  sensitiser, levosimendan, ultimately increase sarcoplasmic  $\text{Ca}^{2+}$  concentration in vascular smooth muscle or cardiac muscle via the various receptors and second messenger pathways described in standard texts. Most of the available agents in South Africa are adrenoceptor agonists. Excessive intracellular  $\text{Ca}^{2+}$  can activate the apoptotic pathways.

## Appropriate targets

Optimal resuscitation requires goal-directed administration of a synergistic balance of fluids, vasopressors and inotropes to correct the combination of intravascular volume deficit, vasodilation and cardiac dysfunction present in the individual patient at that specific time. Adverse effects are predictable if the balance is wrong. Side-effects are amplified if more of the agent is given than strictly required to achieve an adequate life-sustaining circulatory target. Thus, the first practical management step is to define haemodynamic targets that “should be just enough to sustain life”.

Mean arterial pressure (MAP), the driving pressure for blood flow into most organs, is easy to measure and use as a target. Based on available (weak) evidence, the adult Surviving Sepsis Campaign guidelines recommend that a MAP target of 65 mmHg is adequate to perfuse previously normal kidneys, and by implication most other organs, unless they are in closed compartments with elevated compartment pressure when higher MAP targets may be justified.<sup>1</sup> Using a MAP target is adequate if there is only one active mechanism of shock. But since  $\text{MAP} = \text{cardiac output} \times \text{systemic vascular resistance (SVR)}$ , and cardiac output is itself a result of fluid status (preload), contractility and factors that affect myocardial wall tension (afterload) using MAP as a sole target may be dangerously misleading when several shock mechanisms coexist and abnormalities (with divergent effects on MAP) mask each other. Avoiding this trap is easier if cardiac output is monitored. Now that a range of relatively easy-to-use cardiac output monitoring devices is available, an adequate cardiac output will become a co-target, alongside an adequate MAP. Cardiac output targets are still debated, and probably vary across pathologies, but a cardiac index that is any lower than  $2.2 \text{ l/minute/m}^2$  is probably inadequate in many patients. The debate over the priority of cardiac output versus MAP is pointless. Organs such as the kidneys clearly require both a good cardiac output and a good MAP.

## General considerations

Most vasopressors and inotropes have short half-lives (around 45 seconds for adrenaline), and thus require continuous regulated infusion, but this gives the benefit of titrability. A maximum dose of drugs working via cell surface receptors, such as catecholamines (which work via adrenoceptors), must exist in each patient and correspond to 100% receptor occupancy, beyond which escalation is futile. Unfortunately, these maxima vary between patients.

Co-infusion of agents acting on the same receptors, such as adrenaline and phenylephrine, which both stimulate  $\alpha_1$ -adrenoceptors, is entirely feasible to allow specific titration of cardiac output and SVR, but is only possible when each agent is given at “submaximal” doses. Upward titration to effect is generally recommended, as many agents show hysteresis. The effect of a certain plasma level may be different when that plasma level follows a previously higher level than when that same level follows escalation from a lower level.

## Pure inotropes

Dobutamine is a beta 1- and beta 2-cardiac adrenoceptor agonist that affords positive inotropy with limited chronotropy. Skeletal muscle arterioles may be dilated by peripheral beta 2 effects, hence the “inodilator” label. Thus, dobutamine as the sole agent is appropriate for conditions of low cardiac output and elevated SVR, such as decompensated left ventricular failure and cardiogenic shock, when the patient is fluid replete or fluid overloaded. Dobutamine is also appropriate, in conjunction with purposeful adequate fluid resuscitation and vasopressor use, in the “cold” vasoconstricted low cardiac output variant of septic shock.<sup>1</sup> But if given in the presence of uncorrected fluid depletion, or of significant vasodilation, the administration of isolated dobutamine may precipitate hypotensive collapse. Hence, the recommendation is to avoid dobutamine as the initial agent in hypotensive patients with vasodilation or fluid depletion, until these have been addressed by other agents.

Titration of dobutamine doses within the recommended range up to  $20 \mu\text{g/kg/minute}$  against MAP can be difficult as even if cardiac output rises, MAP may decline due to the vasodilation. Thus, cardiac output monitoring is essential if dobutamine is used in mixed-mechanism shock to specifically augment cardiac output. Use of any inotrope in patients with cardiogenic shock from myocardial ischaemia requires particularly cautious titration to conservative cardiac output and MAP targets to avoid worsening of ischaemic damage by an excessive increase in myocardial workload.

Phosphodiesterase inhibitors, such as milrinone, have broadly similar effects to dobutamine, although vasodilation, especially pulmonary vasodilation, tends to be more prominent, and for licensing reasons, phosphodiesterase inhibitors are only available in specialist cardiac centres.

## Pure vasopressors

Phenylephrine, an  $\alpha$ -adrenoceptor agonist, is the most commonly used pure vasopressor on the South African market as vasopressin is not available, and use of ornipressin as a systemic vasopressor is off label. Isolated vasopressor usage is logical when the sole active shock mechanism is vasodilation and distributive shock. Hence, phenylephrine administration constitutes best

practice in hypotensive fluid-replete obstetric patients after subarachnoid block. Vasopressors given at a low dose may constrict abnormally dilated venous beds, minimising pooling of blood and improving cardiac preload. At a higher dose, they augment arteriolar tension and counteract arteriodilation. It might appear logical to add phenylephrine to submaximal doses of adrenaline to more efficiently reach MAP targets in profoundly vasodilated patients with a measured high cardiac output, but otherwise phenylephrine is not recommended by the Surviving Sepsis Campaign.<sup>1</sup> Routinely administering phenylephrine to hypotensive anaesthetised patients can be dangerous. High doses of phenylephrine can generate high MAPs from arterioconstriction, even in critically hypovolaemic patients; can critically reduce cardiac output and precipitate cardiac failure by imposing an excessive cardiac afterload; and can aggravate gut and extremity ischaemia. Many agents used in general anaesthesia are negatively inotropic, and the inflammatory response to surgery or sepsis may cause myocardial dysfunction. Therefore, usage of phenylephrine above minimal doses in nonobstetric anaesthesia must be accompanied by active correction of fluid deficit and diligent cardiac output monitoring.

### Multipotent agents

An “all-in-one” drug that combines inotropic and vasopressor activity is convenient for most patients with multi-mechanism shock, such as those presenting for surgery for delayed trauma or sepsis, but with the caveat that the inotropy to vasopressor ratio may not be ideal for the individual patient and the ratio typically varies as the dose is varied.

The theoretically ideal agent for typical vasodilated septic shock, as recommended by the Surviving Sepsis Campaign, is noradrenaline (norepinephrine), which has a moderate inotropic effect from beta 1-adrenoceptor agonism, coupled with effective vasoconstriction due to alpha 1-adrenoceptor agonism.<sup>1</sup> However, noradrenaline is not available in South Africa.

Dopamine is a time-honoured alternative that stimulates both the beta 1- and alpha 1-adrenoceptors, but it has many problems that make its ongoing use controversial. It is now only recommended by the Surviving Sepsis Campaign in restricted circumstances.<sup>1</sup> Much of its action is indirect via

displacement of endogenous noradrenaline from the nerve terminals, hence it fails in maximally stressed patients with endogenous catecholamine exhaustion. It suppresses thyroid-stimulating hormone release, increases infection rates via prolactin suppression, worsens splanchnic ischaemia, and any supposed benefit of dopamine 1 receptor-mediated renal artery dilation is nullified by intrarenal shunting. The observed improved urine output is owing to a diuretic-like effect. In short, dopamine is not renoprotective.<sup>2</sup>

Adrenaline (epinephrine) is the most commonly used mixed vasopressor-inotrope in South Africa. It is potent, direct-acting, rapidly titratable, readily available and cheap. Titrated within a typical dosing range of 0.05–1 µg/kg/minute, it is undeniably effective in younger patients with sepsis and trauma, but its problems must be recognised. It causes excessive tachycardia as it stimulates both beta 1- and beta 2-adrenoceptors in the heart, which may aggravate myocardial ischaemia and increase arrhythmia risk. Beta 2-adrenoceptor-mediated peripheral vasodilation offsets some alpha 1-adrenoceptor-mediated vasoconstriction, hence there is relatively inadequate vasoconstriction comparative to inotropy for many patients with predominantly distributive shock. Adrenaline drives hyperglycaemia and hyperlactataemia. While hyperlactataemia is predominantly the consequence of adrenaline-accelerated glucose breakdown, and is often felt to be benign, it confuses the use of lactate as a marker of tissue perfusion adequacy. There are also still concerns regarding adrenaline as an aggravator of tissue ischaemia. The available studies fail to demonstrate the inferiority of adrenaline when it is compared to noradrenaline,<sup>3</sup> so it is reasonable to say that used with careful monitoring, titrated to reasonable MAP and cardiac output goals, in conjunction with careful fluid administration, the benefits of adrenaline generally outweigh the risks.

### References

1. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med.* 2013;41(2): 580-637.
2. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest.* 2003;123(4):1266-1275.
3. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet.* 2007;370(9588):676-684.