

The ATHOS-3 trial, angiotensin II and *The Three Musketeers*

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Hypotension is the defining haemodynamic marker of shock in general, and of septic shock in particular, and is the target of therapeutic interventions worldwide.¹ The aim of such interventions is to restore blood pressure deemed sufficient to maintain vital organ perfusion, while interventions treating the underlying cause of shock are being implemented. In the case of septic shock or other forms of inflammatory vasodilatory shock, interventions applied to restore adequate blood pressure typically include rapid administration of intravenous fluid (fluid bolus therapy [FBT]), administration of a vasopressor drug, or both.¹

The rapid administration of fluid in septic shock is based on the notion that vasodilatation and increased capillary leakiness lead to intravascular fluid depletion, which in turn causes decreased cardiac output. This, again in turn, is thought to be partly responsible for the hypotension observed and for most of the decreased tissue perfusion. Such decreased tissue perfusion is inferred from the presence of hyperlactataemia, oliguria, decreased renal function, altered mental state, decreased capillary refill time and mottled skin.² This paradigm is attractive and simple. However, like all simple explanations for complex phenomena, it is open to challenge. In particular, the native (pre-resuscitation) cardiac output in septic shock may actually be preserved or even supranormal;³ the elevated lactate may represent the metabolic expression of an increase in adrenergic state;⁴ oliguria and loss of renal function may represent intrarenal shunting⁵ rather than decreased perfusion; and, similarly, the cerebral and cutaneous manifestation of shock may also represent microvascular shunting. All these conditions may well be unresponsive to FBT. In the simple case of hypotension, the evidence is that any effect of FBT is minimal, dissipates rapidly and is typically undetectable 1 hour after a given bolus.⁶⁻⁸

Faced with such lack of efficacy, in patients for whom hypotension is considered too severe to be tolerated, clinicians typically turn to the use of vasopressors. Vasopressors are reliably efficacious in restoring blood pressure and certainly much more so than FBT.⁹⁻¹² Among clinically available vasopressors, three agents, like the formidable three musketeers of Alexandre Dumas' book, have dominated the therapeutic armamentarium: epinephrine (adrenaline), norepinephrine (noradrenaline) and vasopressin (arginine vasopressin). These agents are used by clinicians, alone or in combination, to maintain macro-haemodynamic stability. This stability is defined by

adequate cardiac output and mean arterial pressure and, it is hoped, evidence of stable or improving vital organ function and markers of microvascular recovery.

In *The Three Musketeers*, each of the three, however skilled with the sword, had serious character flaws; and in the end there were four. Epinephrine, like the impetuous d'Artagnan, can deliver combined alpha and beta effects promptly. However, the effects are accompanied by tachycardia, hyperglycaemia, hyperlactataemia, increased risk of arrhythmia and potentially adverse effects on renal perfusion.^{13,14} Norepinephrine, like the muscular Porthos, can deliver blood pressure control under almost all circumstances, but it may induce myocardial cell band necrosis, increase the risk of atrial fibrillation, induce cutaneous vasoconstriction and digital hypoperfusion, and may decrease renal medullary oxygenation.^{15,16} Vasopressin, like the sophisticated Aramis, typically reflects a greater level of nuanced haemodynamic management delivered in the intensive care unit. However, it also carries risks and limitations, such as its profound splanchnic vasoconstrictive effects and the limited ability to titrate it beyond an upper fixed-dose range. Despite promising early evidence, a large randomised controlled trial testing its effectiveness failed to identify a beneficial effect on patient-centred outcomes in septic shock.¹²

In this context, the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) trial, named after the oldest and most secretive remaining musketeer, matters a great deal. Recruitment for the trial was recently completed and involves about 75 ICUs worldwide, including multiple sites in Australia and New Zealand. The ATHOS-3 trial introduces another powerful vasopressor agent, angiotensin II (ANG II). In the trial, as described in the protocol and statistical analysis plan and as reported in this issue of the Journal,¹⁷ ANG II was compared with placebo as an adjunctive vasopressor in patients requiring a catecholamine dose > 0.2 mg/kg/min. Started at 20 ng/kg/min, the dose was titrated according to a strict protocol with a haemodynamic primary endpoint, as prescribed by the US Food and Drug Administration (FDA), and with change in Sequential Organ Failure Assessment score as a secondary outcome.

The application of ANG II to the management of vasodilatory shock is physiologically logical. ANG II is one of the four vasoconstrictive hormones secreted in response to shock in order to defend blood pressure (epinephrine, norepinephrine, vasopressin and ANG II). It is also not new;

previous uncontrolled studies have reported the efficacy of ANG II as a vasopressor and have not reported unexpected safety concerns.⁹⁻¹¹ Moreover, animal studies have reported efficacy in restoring urinary output and creatinine clearance in a model of septic shock.¹⁸ Finally, assessment of renal bioenergetics during its infusion has dispelled concerns that its vasoconstrictive effect on the efferent glomerular arteriole would induce marked renal tissue hypoxia.¹⁹

What is new is that, if the ATHOS-3 trial shows both safety and efficacy, it will provide the ICU community with likely FDA approval for the use of ANG II in vasodilatory shock. For the Australian and New Zealand community, Therapeutic Goods Administration approval would likely then follow and make the agent available to local clinicians. Such availability may lead to “balanced” vasopressor therapy, which, by combining at least three of the vasoactive musketeers (ANG II, vasopressin and norepinephrine) will attempt to simulate the typical physiological response to severe vasodilatation and hypotension. This balanced vasopressor therapy might also compensate for its limited ability to deal with severe overwhelming vasodilatation, maximise efficacy and minimise toxicity. Combined with appropriate inotropic support in cases of myocardial depression, this approach may prove physiologically optimal. If so, a true phase III trial with patient-centred outcomes may well follow. Like the fate of Cardinal Richelieu at the end of *The Three Musketeers*, religious use of FBT will be challenged by the need to treat the three, and now four, vasopressors with greater respect.

Competing interests

None declared.

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References

- 1 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315: 801-10.
- 2 Rivers E, Nguyen B, Havstad S, et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368-77.

- 3 Cioccarl L, Luethi N, Weber U, et al. The native cardiac output in human sepsis: a systematic review. *Crit Care Resusc* 2016; 18: 148-56.
- 4 Garcia-Alvarez M, Marik P, Bellomo R. Sepsis-associated hyperlactatemia. *Crit Care* 2014; 18: 503.
- 5 Bellomo R, Wan L, Langenberg C, May C. Septic acute kidney injury: new concepts. *Nephron Exp Nephrol* 2008; 109: e95-100.
- 6 Lipcsey M, Chiong J, Subiakto I, et al. Primary fluid bolus therapy for infection-associated hypotension in the emergency department. *Crit Care Resusc* 2015; 17: 6-11.
- 7 Lipcsey M, Subiakto I, Chiong J, et al. Epidemiology of secondary fluid bolus therapy for infection-associated hypotension. *Crit Care Resusc* 2016; 18: 165-73.
- 8 Bannard-Smith J, Alexander P, Glassford N, et al. Haemodynamic and biochemical responses to fluid bolus therapy with human albumin solution, 4% versus 20%, in critically ill adults. *Crit Care Resusc* 2015; 17: 122-8.
- 9 Thomas VL, Nielsen MA. Administration of angiotensin II in refractory septic shock. *Crit Care Med* 1991; 19: 1084-6.
- 10 Cohn JN, Luria MH. Studies in clinical shock and hypotension. II. Hemodynamic effects of norepinephrine and angiotensin. *J Clin Invest* 1965; 44: 1494-504.
- 11 Chawla LS, Busse LW, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS Trial): a pilot study. *Crit Care* 2014; 18: 534.
- 12 Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; 358: 877-87.
- 13 Myburgh JA, Higgins A, Jovanovska A, et al. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med* 2008; 34: 2226-34.
- 14 Bellomo R, Wan L, May C. Vasoactive drugs and acute kidney injury. *Crit Care Med* 2008; 36 (4 Suppl): S179-86.
- 15 Asfar P, Meziani F, Hamel JF, et al. High versus low blood pressure target in patients with septic shock. *N Engl J Med* 2014; 370: 1583-93.
- 16 Lankadeva YR, Kosaka J, Evans RG, et al. Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int* 2016; 90: 100-8.
- 17 Chawla LS, Russell JA, Bagshaw SM, et al. Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3): protocol for a phase III, double-blind, randomised controlled trial. *Crit Care Resusc* 2017; 19: 43-49.
- 18 Wan L, Langenberg C, Bellomo R, May CN. Angiotensin II in experimental hyperdynamic sepsis. *Crit Care* 2009; 13: R190.
- 19 May CN, Ishikawa K, Wan L. Renal bioenergetics during early gram-negative mammalian sepsis and angiotensin II infusion. *Intensive Care Med* 2012; 38: 886-93. □