An appraisal of selection and use of catecholamines in septic shock — old becomes new again

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The pharmacological support of the failing circulation is fundamental to critical care medicine. Drug strategies to augment and maintain adequate circulatory function have evolved from anecdotal clinical experience and a substantial body of basic scientific literature dating back to the 1950s. However, although use of cardiotropic and vasoactive drugs has been established for the past 25 years, few high quality clinical studies provide unequivocal data on their efficacy and effectiveness on resolution and outcomes from circulatory failure. The development of "best practice" evidence-based guidelines, which form the basis of "treatment bundles", is a challenge to clinicians. While these guidelines synthesise the published evidence for treatment modalities in complex conditions such as sepsis and septic shock, their applicability and generalisability depend on the quality of the available evidence and integrity of the resulting recommendations.

Interpreting the literature on the use of cardiovascular drugs is confounded by a number of factors. Firstly, the nomenclature and classification of these drugs vary widely. They are usually classified as inotropes (drugs that primarily act on the heart — positive inotropic agents) or vasopressors (drugs that act primarily on the vasculature — arterial vasoconstrictors), but this distinction assumes they have specific and predictable pharmacodynamic effects. Secondly, there is no consensus as to which haemodynamic or systemic end-points should be targeted to optimise impaired circulatory function or to resuscitate in circulatory failure arising from different causes.

This review addresses the evidence for the selection and use of cardiovascular drugs in septic shock, in the light of the above factors.

Drug structure–function relationships

The most frequently used inotropes/vasopressors in the intensive care unit are the sympathetic amines. These include the naturally occurring catecholamines (noradrenaline, adrenaline and dopamine) and synthetic substances (dobutamine, isoprenaline, dopexamine, milrinone and levosimendan).[1]

Considering the action and effects of these drugs requires an appreciation of the biology of the naturally occurring compounds and the chemical structure of the synthetic compounds.

ABSTRACT

The use of catecholamines to defend and resuscitate patients with septic shock remains a cornerstone of intensive care medicine. The pharmacological support of the failing circulation during sepsis and septic shock should be directed at augmenting perfusion of vital organs and facilitating venous return, rather than peripheral arterial vasoconstriction. There appears to be a teleological rationale for primary use of catecholamines to augment failing endogenous neurohumoral and neuroendocrine cardiovascular systems. To this end, it seems intuitive to use the predominant naturally occurring catecholamine, noradrenaline, as the first-line agent for circulatory failure, although there are no definitive clinical trials to support this. Adrenaline has an established place in many parts of the world, particularly low-income countries, and appears to be equivalent to noradrenaline for reversing septic shock.

There is increasing evidence for adverse neuroendocrine and immunological effects of dopamine, warranting circumspection about its use. The use of synthetic inotropes and vasopressors for septic shock remains limited, with little biological rationale. Clinicians should wait for definitive outcome-based trials of these expensive agents before incorporating them into practice. Supplemental endocrine replacement therapy with low-dose corticosteroids and vasopressin appears biologically plausible and has an emerging role.

Results of large-scale, high-quality trials of endogenous catecholamines for sepsis and septic shock are awaited. These may provide additional, important information for evidence-based guidelines, which currently remain of limited clinical utility.
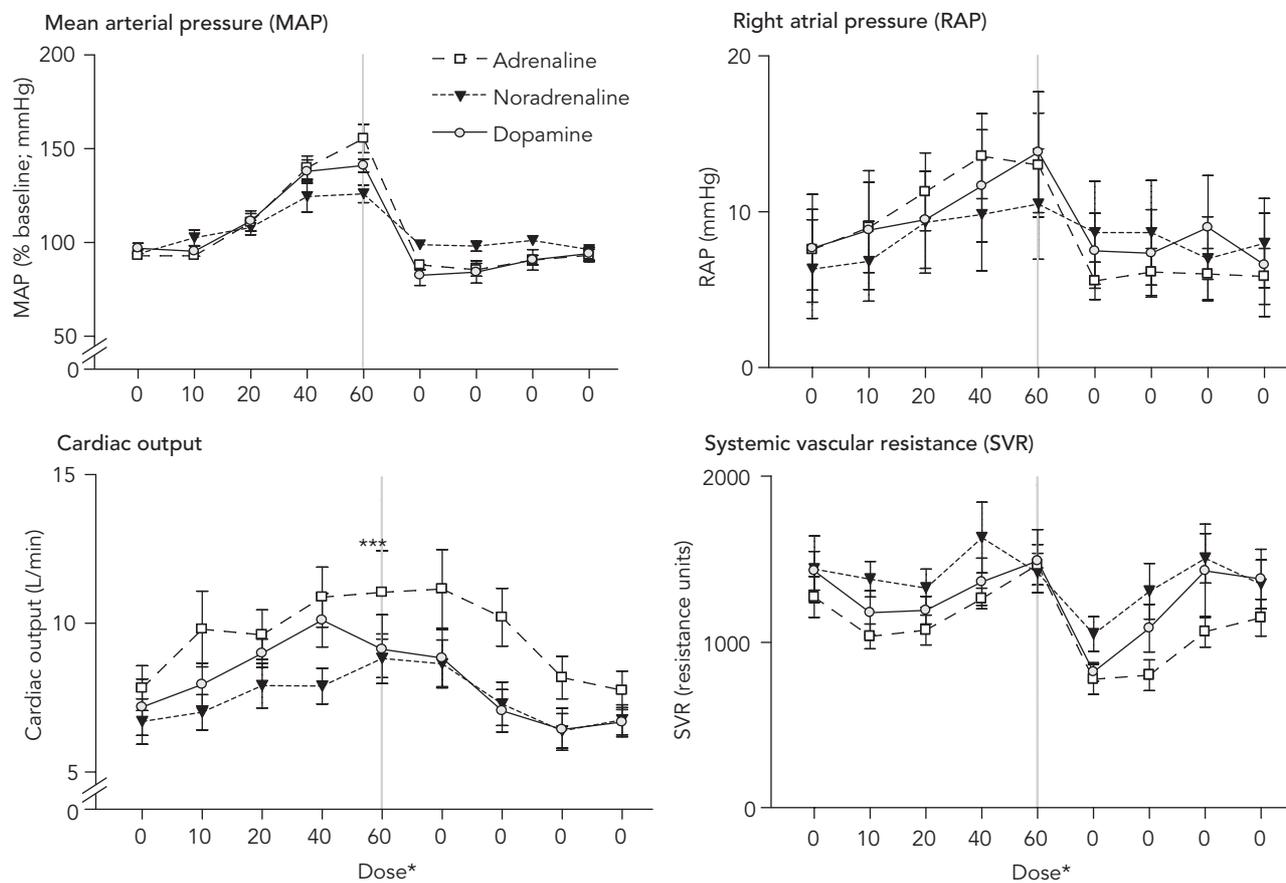
Naturally occurring catecholamines

Dopamine is a prehydroxylated noradrenaline precursor. The release of noradrenaline from sympathetic nerve terminals is controlled by re-uptake mechanisms and augmented by the adrenal release of adrenaline during stress.[2] There is therefore a teleological basis for exogenous administration of dopamine and adrenaline, acting primarily through

Figure 1. Effects of adrenaline, noradrenaline and dopamine on cardiovascular parameters in a physiological ovine preparation

Mean arterial pressure (MAP)

Right atrial pressure (RAP)

Cardiac output

Systemic vascular resistance (SVR)

*Dose is expressed as μg/min for noradrenaline and adrenaline, and μg/kg/min for dopamine. Data are expressed as mean ± SEM. *** = P < 0.001. [11] ◆
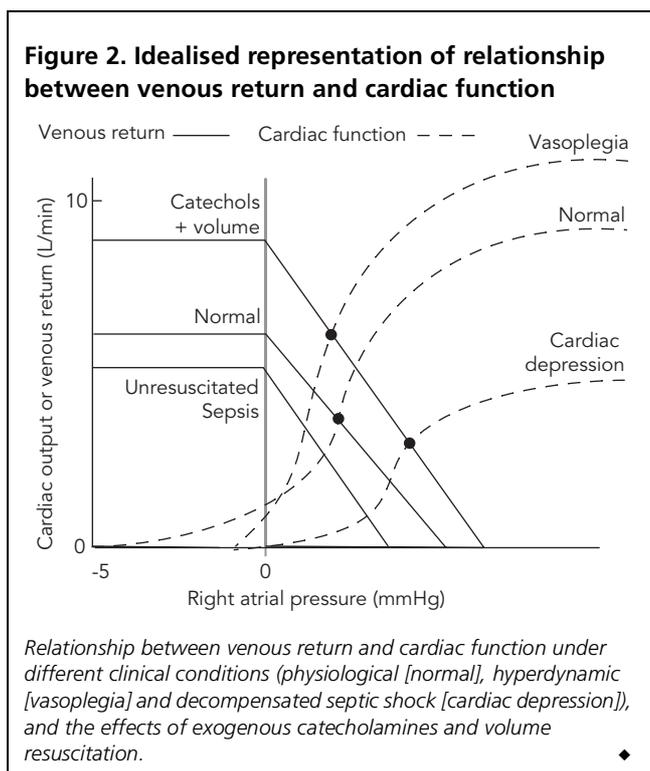
increasing and augmenting the release of noradrenaline, producing blood concentrations similar to those produced endogenously in shock. All catecholamines have very short biological half-lives (1–2 minutes), and a steady-state plasma concentration is achieved within 5–10 minutes from the start of a constant infusion. This allows rapid dose titration.

Noradrenaline is the predominant endogenous sympathetic amine acting at all populations of adrenoreceptors. There is a common misperception that it is predominantly an α-agonist, but this is not substantiated in the biological literature. Many of the perceived specific actions of catecholamines originate in textbook discussions that link structure to function and preferential effects on adrenergic receptors.

An expanding population of adrenergic receptors (α_{1A} and α_{1B}, α_{2A}, α_{2B}, and α_{2C}, β_1, β_2 and β_3) has been identified.[3] Signal transduction from agonist-receptor occupation to the effector cell is modulated by conformational changes in G proteins. Under the additional influ-

ence of second messengers, these conformational changes induce phosphorylation of substrate proteins, which act as third messengers to trigger a cascade of events leading to specific cardiovascular effects.[3] Importantly, the activity and function of this system is dynamic and may be markedly influenced by pathological states such as sepsis, resulting in qualitative (desensitisation) and quantitative (down-regulation) changes in the agonist–receptor–effector relationship.[4] Cardiovascular effects vary markedly and unpredictably between and within individuals under physiological and pathological conditions.

This complex and dynamic system is far removed from the two-dimensional agonist–effector relationship described in most textbooks. This was based largely on a few volunteer studies conducted in the 1950s–1970s, using disparate doses of drug and indirect measurements.[5-7] In these early studies, the observed effects of noradrenaline, adrenaline and isoprenaline on blood pressure, heart rate and total peripheral resistance were interpreted according to the then

Figure 2. Idealised representation of relationship between venous return and cardiac function

Venous return ——— Cardiac function – – –

Relationship between venous return and cardiac function under different clinical conditions (physiological [normal], hyperdynamic [vasoplegia] and decompensated septic shock [cardiac depression]), and the effects of exogenous catecholamines and volume resuscitation. ◆

knowledge of adrenergic receptor biology (for which some studies received the Nobel Prize[8]). Regrettably, the translation into clinical research and practice has lagged behind the advances in biological research on adrenoreceptors and signal transduction.

Few studies directly compare the pharmacodynamic effects of catecholamines using comparable doses and reproducible physiological measurements. In a physiological sheep preparation, the effects of ramped infusions of adrenaline and noradrenaline (0–60 μg/min) and dopamine (0–60 μg/kg/min) on systemic haemodynamics were determined[9,10] (Figure 1). All three drugs significantly and equivalently increased mean arterial pressure, cardiac output and right atrial pressure in a dose-dependent manner from baseline, without demonstrable changes in systemic vascular resistance or heart rate. Beta-effects tended to predominate at low doses, while α-effects predominated at higher doses. These data provide clear evidence of the equivalent effects of exogenous catecholamines under physiological conditions.

The distinction between "inotropes" and "vasopressors" is therefore somewhat artificial, particularly when the term "vasopressor" is used to define arterial vasoconstriction. All catecholamines have both cardiotropic and peripheral vascular effects, and it is impossible to predict which drug action will predominate in an individual patient, particularly during illness.

Synthetic catecholamines and non-catecholamines

The synthetic catecholamines dobutamine, isoprenaline and dopexamine are derivatives of dopamine, characterised by an increased length of the carbon chain, which primarily confers affinity for β receptors, thereby producing predominant vasodilatation and modest inotropy. These agents have relatively little affinity for α receptors, due to the configuration of the terminal amine, which differs from that in the endogenous catecholamines.[2]

Synthetic non-catecholamines, such as milrinone and levosimendan, act via mechanisms independent of cyclic-AMP-mediated changes in adenyl cyclase activity, with predominant lusitropic and vasodilatory actions, respectively. The biological half-lives of these drugs are 20–30 minutes, and longer in renal failure, limiting their usefulness as infusions. Hypotension is commonly associated.

Pathophysiology of sepsis and septic shock

Physiologically, haemodynamic function is represented as the balance between cardiac output and venous return.[12-14] In effect, the arterial and venous circulations exist in parallel, so that significant changes in one circulation are balanced by compensatory changes in the other. This relationship is shown in Figure 2.

The arterial circulation is represented as an aggregated myocardial systolic and diastolic function curve (L/min), and the venous circulation as the mean rate of venous return from the periphery. The gradients down which these two circulations flow are distinctly different. The arterial circulation is primarily a conduit (containing 10% of the circulating blood volume), providing convective substrate delivery to the tissues. The arterial pressure gradient depends on myocardial ejection (contractility) and end-organ afferent arteriolar tone. Accordingly, there is only a modest drop in mean arterial pressure gradient between the heart and the periphery. The major fall in systemic pressure occurs across end-organ microvasculature (Δ50–60 mmHg), and bears little relationship to afferent conduit pressure and flow.

The mean systemic pressure generated when de-oxygenated blood exits the microvasculature represents the principal afferent gradient before the onset of venous return to the heart. The venous circulation (containing 70% of the circulating blood volume) operates at a substantially lower pressure gradient (Δ10 mmHg), but is able to match abrupt changes in cardiac output driven by metabolic demand. This is achieved by intense neurohumoral-induced changes in venous tone mediated by populations of adrenergic receptors, and the influences of circulating hormones, such as cortisone, vasopressin and endothelin. Consequently, the venous circulation represents an endogenous reservoir of blood, capable of delivering additional blood to maintain

atrial preload under "stressed" and "non-stressed" conditions. This is one of the principal determinants of ventricular contractility and ejection.

The interception of the cardiac output and venous return curves depicted in Figure 2 represents the balance between the two circulations at any time point. Theoretically, this point represents the optimal target for monitoring or resuscitating the circulation. However, the ability to determine this point at the bedside remains elusive. Although a number of surrogate end-points have been advocated (such as mean arterial pressure, cardiac output/oxygen delivery, right atrial pressure and oxygen extraction ratio), it is apparent that no single parameter can represent this complex biological system. Accordingly, assessment of haemodynamic function under conditions of circulatory failure requires integration of a number of clinical end-points, assessed within the context of the underlying pathological processes.

The effects of sepsis and septic shock on this relationship are presented in Figure 2.[13] The haemodynamic perturbations in sepsis are complex and vary between patients. They affect the arterial and venous circulations equally. Initially, the haemodynamic effects of sepsis manifest as a hyperdynamic "vasodilated" state. The hallmark of this early phase is increased metabolic demand from sepsis-induced inflammatory mediators, resulting in compensatory increases in cardiac output and venous return. An associated reduction in neurohumoral venous vasoresponsiveness results in venous pooling and relative hypovolaemia, which is initially matched by compensatory increases in heart rate, although this usually manifests clinically as systemic hypotension. In the early phases of sepsis, about 20% of patients will respond to volume resuscitation. Septic shock ensues when the septic process induces systolic and diastolic myocardial dysfunction, resulting in impaired ventricular ejection, and neurohumoral paralysis of the peripheral vasculature (vasoplegia), which predominantly affects the venous circulation, resulting in markedly reduced venous return, cardiac output and mean arterial pressure. While arterial vasodilatation is also a feature of sepsis and septic shock, it is chiefly a compensatory mechanism to augment cardiac output, and not a principal component of the "vasoplegic" state. Resultant pathological hypotension (septic shock) primarily represents the inability of the circulation to respond to endogenous neurohumoral and neuroendocrine stimulation.

In the failing myocardium, particularly in patients with cardiac failure after cardiopulmonary bypass or septic shock,[15] endogenous stores of noradrenaline are markedly reduced. Furthermore, there may be significant desensitisation and down-regulation of cardiac β receptors.[16] In these situations, α_1 and α_2 receptors have an important role in maintaining inotropy and peripheral vasoresponsiveness.[17] This may be expressed clinically as "tolerance" or tachyphylaxis to catecholamines, particularly with predominant β-agonists, such as dobutamine, isoprenaline and dopexamine. This phenomenon may explain the requirement for high doses of these catecholamines in refractory shock states. Consequently, the role of β-agonists in patients with severe myocardial failure has been questioned.

The predominant vascular effect of catecholamines is on the venous circulation. These drugs primarily restore or maintain "stressed volumes" of the capacitance vessels under pathological conditions, thereby maintaining or increasing cardiac output and mean arterial pressure. In clinical doses, intravenously administered catecholamines have minimal direct vasoconstrictive effects on conducting arterial vessels. Consequently, derived indices such as systemic vascular resistance do not reflect the effect of catecholamines on the peripheral vasculature. Systemic vascular resistance is a derived index based on Ohm's law defining electrical current through a conductor of uniform length and diameter. This concept has little physiological relevance to pulsatile haemodynamic flow in the arterial and venous circulations. Despite this, systemic vascular resistance is commonly, and erroneously, used by clinicians as an index of vascular tone under conditions of circulatory failure, and indeed is often used as a diagnostic criterion for severe sepsis and septic shock. There is no single haemodynamic end-point that accurately reflects the severity of sepsis or adequacy of response to resuscitation.

The development of peripheral gangrene in refractory septic shock has been attributed to catecholamine-induced arterial vasoconstriction. There is little evidence to support this, as tissue gangrene in this situation is primarily a consequence of intravascular thrombosis caused by sepsis-mediated coagulopathy.

Recent awareness of neuroendocrine function in sepsis has identified functional or absolute hypoadrenalism[18] and hypovasopressinaemia[19] in sepsis and septic shock. This frequently presents as "catecholamine-resistant" shock, defined by the need for escalating doses of exogenous catecholamines to produce a target mean arterial pressure or cardiac output. The use of replacement doses of hydrocortisone and vasopressin has become commonplace to improve catecholamine vasoresponsiveness and, while there are limited studies of the effectiveness of these strategies to improve outcome, there appears to be a reasonable physiological rationale for their use in selected patients with sepsis and septic shock.

From the above discourse, it is clear that the haemodynamic effects of sepsis and septic shock are complex. Haemodynamic responses vary within and between individ-

uals, depending on the impact of the septic process on neurohumoral and neuroendocrine function.

The evidence for catecholamines in septic shock

Given the extensive physiological and pathophysiological understanding of catecholamines and the cardiovascular perturbations of sepsis and septic shock, there appears compelling justification for the use of endogenous catecholamines, particularly noradrenaline or adrenaline, for resuscitation in sepsis and septic shock, possibly augmented with endocrine replacement therapy in selected patients. There appears little rationale for the use of synthetic agents, such as dobutamine. This assumption is not reflected in the literature, and there is a paucity of evidence on which to base clinical judgement.

The reasons for this vary. Most studies of inotropes/vasopressors in animal models of sepsis or human observational or case–control series used surrogate outcome measures. In the 1990s, many of these studies were directed at identifying the most reliable and predictable physiological end-points as targets for resuscitation — most commonly, mean arterial pressure, systemic vascular resistance and cardiac indices, and metabolic indices such as oxygen delivery, oxygen consumption, intramucosal pH and serum lactate concentration.

Dopamine was the most commonly used agent, perhaps reflecting regional preferences, particularly in North America, where noradrenaline was used sparingly and often reserved for cases of refractory shock. These studies were confounded by wide variations in dose and timing of use, small patient numbers and variable end-points, but provided some information about dose–response and side effects. There appeared some consistency in reporting equivalent augmentation of mean arterial pressure and cardiac output with noradrenaline, adrenaline and dopamine in sepsis.

Evidence about potential adverse effects of dopamine have emerged, with demonstration of dopamine-induced inhibition of pituitary function and reduction in T-cell function.[20,21] The role of dopamine as a renal protective agent was refuted in a large randomised controlled trial,[22] and recent evidence from an observational European study suggested that dopamine use was associated with higher mortality in patients with septic shock.[23]

Limited studies of adverse metabolic effects of adrenaline raised concerns about lactic acidosis, particularly in severe sepsis, as in malaria.[24] However, other studies have confirmed that adrenaline-induced hyperlactaemia is primarily a transient phenomenon associated with inhibition of pyruvate dehydrogenase, and has no relationship with cellular hypoxia or associated metabolic acidosis.[25] A number of studies analysed the effects of catecholamines on gut function, most using intramucosal pH as a surrogate index of gut mucosal perfusion. These studies had conflicting results, with little evidence of an association with gut ischaemia or catecholamine-induced gut "protection" for drugs such as dopexamine.[26]

Most clinical studies during the 1990s were directed at identifying a relationship between haemodynamic augmentation to attain target levels of oxygen delivery and improved outcome from sepsis and septic shock.[27] This strategy was predicated on the hypothesis that one of the principal perturbations of sepsis and septic shock is impaired oxygen extraction and utilisation, and that "boosting" the circulation to maximise convective oxygen delivery will improve outcome. In these studies, dobutamine and dopexamine were the most commonly used drugs, again largely reflecting regional practice (and possibly the influence of pharmaceutical marketing). Initial limited studies had positive outcomes, but the strategy was discredited by the publication of equivocal and negative trials and the increasing recognition that achieving "supranormal" convective oxygen delivery did not improve or sustain vital organ function.[28,29] Furthermore, the use of synthetic drugs such as dobutamine and dopexamine in sepsis seems counterintuitive, given the predominant β-adrenergic effects under conditions where there is rapid β– (and α–) receptor down-regulation and desensitisation, and the limited role of β-receptor function in augmenting cardiac function and venous return.

The "dobutamine/dopexamine oxygen delivery" focus dominated the literature on inotropes/vasopressors in sepsis and septic shock for most of the 1990s. There were few studies that analysed the efficacy and effectiveness of other catecholamines, despite their ubiquitous use in many parts of the world, particularly in the southern hemisphere. A review of the predominantly North American literature in 1996 identified four clinical studies of adrenaline in sepsis and septic shock (total, 56 patients) and eight studies of noradrenaline (total, 162 patients), compared with 11 studies of dobutamine (representing 396 patients).[30] All these studies were considered to be limited in methodological design, with disparate dose ranges and end-points, and wide ranges of mortality. Despite these limited studies, an increasing body of literature now supports the use of noradrenaline and adrenaline as first-line agents in sepsis and septic shock to effectively defend cardiac output, mean arterial pressure and thereby tissue perfusion.[31-34] Systemic vascular resistance is not significantly altered by catecholamine infusions in septic shock.[35] Dobutamine and isoprenaline appear to add little to the efficacy of noradrenaline or adrenaline when used in combination.[36]

Infusions of vasopressors, such as phenylephrine[37] and metaraminol, and hormones, such as angiotensin,[38] have been used to augment mean arterial pressure in patients with refractory septic shock with varying degrees of success.

Why is there no definitive study?

Another reason for the lack of a definitive study of catecholamines in sepsis and septic shock may relate to the imperative for the pharmaceutical industry and investigators to conduct trials of widely used, off-patent, cheap drugs. It is not surprising that most of the published clinical studies of catecholamines in sepsis have involved more expensive, synthetic agents (eg, dobutamine, dopexamine, milrinone and levosimendan), thereby reflecting a financially driven publication bias. In addition, few studies of established drugs such as noradrenaline and adrenaline have been funded by peer-reviewed grants, perhaps reflecting a reluctance of major funding agencies to challenge entrenched clinical dogma.

Nevertheless, three large-scale studies of catecholamines are underway in Australia and Europe. The Australian CAT (catecholamine) study is a prospective, multicentre, double-blind, randomised controlled trial of adrenaline and noradrenaline in intensive care patients with shock. The study is stratified by a diagnosis of sepsis, and the primary outcome measure is reversal of shock, defined as attainment of a clinically prescribed mean arterial pressure without catecholamine infusion for > 24 hours. Recruitment was completed in September 2006, and preliminary results presented in October 2006. This study demonstrated no significant difference in the resolution of shock between adrenaline and noradrenaline, although a trend to shorter shock-resolution times and ICU length of stay was observed in patients assigned to receive adrenaline. Furthermore, adrenaline was associated with a transient hyperlactataemia without an associated metabolic acidosis or organ dysfunction.

A second study, from France, is a partial open-labelled study of adrenaline versus noradrenaline plus dobutamine, assessing 28-day mortality in patients with septic shock. Preliminary results were presented in September 2006 demonstrating no significant difference between the two groups. A third study has developed from an observational European study (SOAP — Sepsis Occurrence in Acutely Ill Patients),[39] and is a study of dopamine versus adrenaline as first-line drugs in 1600 patients with hypotension. The study is open-labelled for high-dose noradrenaline (> 20 μg/kg/min) and adrenaline (> 0.19 μg/kg/min), with unrestricted use of other synthetic drugs. Published results are awaited from these larger, higher-quality methodological studies of catecholamines for sepsis and septic shock in intensive care.

The Surviving Sepsis guidelines: do they add up?

Until these studies are published, the clinical literature on sepsis and septic shock will remain dominated by studies of synthetic inotrope/vasopressor drugs. These studies have heavily influenced evidence-based guidelines, such as the Surviving Sepsis guidelines.[40] In many ways, these guidelines represent regional or pharmaceutical-based preferences, rather than a synopsis of the basic science literature. Ultimately, the selection and use of inotropes/vasopressors in sepsis and septic shock requires attention to broader knowledge and experience, rather than guidelines alone.

The following issues should be considered in evaluating the recommendations in the Surviving Sepsis guidelines.

Drug classification

The guidelines present information on "vasopressors" and "inotropes". As outlined above, the distinction between these classes of drugs is largely artificial and entrenches the dogma that drugs used to support the circulation in sepsis have predictable effects on the vasculature and myocardium. The distinction also entrenches the myth that the vascular defect in sepsis is a failure of the arterial circulation. There is strong biological evidence to refute this, but this dogmatic perception of haemodynamic function persists.

Nevertheless, accepting that this classification remains firm in the minds of expert reviewers and clinicians, the guidelines may be considered further.

Either noradrenaline or dopamine is the first-line choice of vasopressor to correct hypotension in septic shock

This powerful statement largely reflects North American and European practice, but the supporting evidence is Grade C (supported by Level II investigation — ie, small randomised trials with uncertain results). The guideline authors recognise that there is no high-quality evidence to recommend one catecholamine over another, but recommend using noradrenaline or dopamine over adrenaline primarily because of the risk of splanchnic ischaemia associated with the latter. This is an unfounded concern based on poor quality studies that used non-validated measurements, and overstates the risk.

This recommendation is problematic, as adrenaline remains the first-line (and only) inotrope/vasopressor in many parts of the world, particularly income-poor countries, where noradrenaline is not available. Furthermore, there is no mention of the higher-quality evidence of neuroendocrine and immunological side effects of

dopamine, which has seen it almost vanish from use in Australia.

Low-dose dopamine should not be used for renal protection as part of treatment of severe sepsis

This recommendation is reported as Grade B (supported by one Level I investigation — a large randomised trial with clear-cut results). This trial was the Australian and New Zealand Intensive Care Society Clinical Trial Group Dopamine study,[22] which has definitively answered the question. Given this important negative trial, the potential side effects of dopamine outlined above, and the observations of dopamine-associated mortality,[23] it is puzzling that dopamine is recommended so strongly above as a first-line vasopressor to correct hypotension in septic shock. This internal inconsistency may again reflect regional and publication bias.

Vasopressin may be considered in patients with refractory shock despite high-dose conventional vasopressors

This recommendation is reported as Grade E (supported by Level IV–V investigations — case series and expert opinion). This is the correct level of evidence for this recommendation. Vasopressin should be reserved for patients with catecholamine-resistant septic shock, although the threshold for its use remains elusive. Within the biological context of this strategy, replacement therapy with low-dose vasopressin appears to have only some validity, although the results of a definitive trial (the VASST study) are awaited.

Dobutamine may be used to increase cardiac output in patients with low cardiac output, and may be combined with vasopressor therapy in the presence of low blood pressure

This is another Grade E recommendation. The paragraph begins by stating that "dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of left ventricular filling (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure". The biological and clinical evidence for this statement is lacking, according with the level E grading, and it may represent regional and publication bias. The biological rationale for using synthetic β-agonists in sepsis remains questionable, and it may represent an (inappropriate) extrapolation from limited studies of acute coronary syndromes. Further, the statement implies that measurement of cardiac output is recommended, but, if not undertaken, that dobutamine be combined with "vasopressor" therapy with noradrenaline or dopamine. Implicit is the recommendation to administer a cocktail of inotropes/vasopressors to patients with sepsis. The pragmatic benefit of this approach, in terms of bedside management, remains questionable.

A strategy of increasing cardiac index to achieve an arbitrarily defined elevated level is not recommended

This is the only Grade A recommendation (supported by two Level 1 investigations) for inotropes/vasopressors. The guideline authors refer to two negative trials of dobutamine to induce supranormal oxygen delivery in sepsis. Given that oxygen delivery is essentially a duplicate measurement of cardiac output, the previous recommendation (to use dobutamine to increase cardiac output) seems illogical.

Summary

The Surviving Sepsis guidelines represent a genuine attempt to collate the published evidence about the use of inotropes/vasopressors in sepsis and septic shock. Not surprisingly, the number and strength of recommendations remain limited, perhaps reflecting the relatively poor state of the published clinical literature. Given this, clinicians are left with recommendations that represent regional (predominantly North American and European) practice. While these may well serve most patients, and are intended to be adjuncts to treatment, rather than prescriptive policies, the gulf between basic scientific evidence and clinical research appears to be widening. In addition to the inevitable "upgrading" of guidelines to become "standards of care", there is a concern that clinicians will move further from interpreting the outcomes of clinical trials with an identifiable biological mechanism. Both of these sequelae may paradoxically reduce critical thought and analysis of practice.

Conclusions

The use of catecholamines to defend and resuscitate the failing circulation during sepsis and septic shock remains a cornerstone of practice. There appears to be a teleological rationale to use these drugs, primarily to augment failing endogenous neurohumoral and neuroendocrine systems. To this end, it seems intuitive to use the predominant naturally occurring catecholamines, noradrenaline or adrenaline as the first-line agent(s) for circulatory failure. Supplemental endocrine replacement therapy with low-dose corticosteroids and vasopressin appears to have an emerging role in this strategy, but requires circumspection. The results of large-scale, high-quality trials of endogenous catecholamines for sepsis and septic shock are awaited. These may provide additional important information for evidence-based guidelines, which remain of limited clinical utility.

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