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REVIEW

Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum

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Abstract

Catecholamines are endogenous neurosignalling mediators and hormones. They are integral in maintaining homeostasis by promptly responding to any stressor. Their synthetic equivalents are the current mainstay of treatment in shock states to counteract myocardial depression and/or vasoplegia. These phenomena are related in large part to decreased adrenoreceptor sensitivity and altered adrenergic signalling, with resultant vascular and cardiomyocyte hyporeactivity. Catecholamines are predominantly used in supraphysiological doses to overcome these pathological consequences. However, these adrenergic agents cause direct organ damage and have multiple 'off-target' biological effects on immune, metabolic and coagulation pathways, most of which are not monitored or recognised at the bedside. Such detrimental consequences may contribute negatively to patient outcomes. This review explores the schizophrenic 'Jekyll-and-Hyde' characteristics of catecholamines in critical illness, as they are both necessary for survival yet detrimental in excess. This article covers catecholamine physiology, the pleiotropic effects of catecholamines on various body systems and pathways, and potential alternatives for haemodynamic support and adrenergic modulation in the critically ill.

Keywords: Catecholamines, Epinephrine, Norepinephrine, Physiology, Pathophysiology, Critical illness, Sepsis

Impact of inflammatory shock on the cardiovascular system

Recognition of pathogen-associated molecular patterns (PAMPs) related to microorganisms and/or release of intracellular damage-associated molecular patterns (DAMPs) from injured cells, such as mitochondria, heat shock proteins and intracellular cytokines, triggers a systemic inflammatory host response [1]. Indeed, DAMPs act through similar receptors to those that recognise PAMPs [2, 3]. This inflammatory response modulates multiple downstream pathways ranging from immune to cardiovascular, hormonal to coagulation, metabolic to bioenergetic [4]. When inflammation is excessive and/or dysregulated, macro- and microcirculatory abnormalities ensue [5]. Myocardial depression, excessive vasodilation and increased capillary leak, resulting in hypovolaemia and tissue oedema, may all impede delivery of sufficient oxygen and substrate to meet cellular metabolic demands. This will be compounded by mitochondrial dysfunction that further compromises ATP production [6]. Cells may defend themselves by reducing metabolic activity to lessen the risk of activating death pathways, but at the cost of a decreased functionality [7]. Therefore, 'inflammatory' shock constitutes the hallmark of sepsis, but also a final common pathway of any form of severe, protracted tissue hypoperfusion or cellular poisoning.

Therapeutic interventions targeting microcirculatory and mitochondrial dysfunction are currently lacking, so management of inflammatory shock focuses on treating the macrocirculatory abnormalities while correcting/removing the underlying trigger event. Hypovolaemia is ubiquitous during the early stages of inflammatory shock, due to both external losses and capillary leak. However, even after volume expansion, patients often remain haemodynamically compromised due to myocardial depression and vasoplegia.

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Myocardial dysfunction is commonplace during shock states. Systolic and diastolic dysfunction occurs in up to 50 and 25 % of patients with septic shock, respectively [8, 9]. Serum troponin and natriuretic peptides are elevated [10, 11] indicative of both myocardial injury and dysfunction, and both prognosticate for poor outcomes. Myocardial dysfunction is usually reversible in survivors of sepsis, with little or no obvious long-term consequences on cardiac function [12]. Several mechanisms contribute to myocardial depression [8], including reduced numbers and functionality of β_1-adrenoreceptors, voltage-activated calcium (Ca^{2+}) channels and ryanodine receptors, resulting in decreased intracellular Ca^{2+} and less actin–myosin cross-bridge formation. In addition, the sarcoplasmic reticulum has reduced Ca^{2+} reuptake affecting diastolic relaxation, while myofibrils show reduced Ca^{2+} sensitivity, and mitochondrial dysfunction makes less energy available for the contraction–relaxation process.

Vascular dysfunction is a hallmark of acute critical illness. Vascular tone and often blood pressure are compromised despite high levels of endogenous and exogenous vasopressors. Mechanisms contributing to vasoplegia include overproduction of vasodilatory mediators, such as nitric oxide and eicosanoids; alterations in the main hormonal axes, with catecholamine hyporesponsiveness, vasopressin deficiency, dysfunction of the hypothalamic–pituitary–adrenal axis and renin–angiotensin–aldosterone system; decreased Ca^{2+}-sensitivity; and activation of vascular smooth muscle ATP-sensitive potassium channels [13–15].

Although the pathogenesis of inflammatory shock is multifactorial and not yet fully understood, it does not include catecholamine deficiency. Endogenous epinephrine and norepinephrine levels in serum are markedly elevated in septic patients [16, 17]. However, catecholamines exert a plethora of other non-haemodynamic effects. They are a key component of the stress response, a finely tuned cardiovascular, metabolic, immune and neurobehavioural process preserved through the course of evolution [18]. While integral to coping with acutely demanding situations, the stress response—and thus catecholamine overload—may be detrimental if its magnitude and/or duration is excessive.

Physiological effects of catecholamines

To better understand how persistently supraphysiological endogenous and/or exogenous catecholamine levels can produce maladaptation in stressful disease states, it is useful to first describe their pleiotropic actions in normal physiology.

Catecholamines function as both neurotransmitters when released into the synaptic space, and hormones when released into the bloodstream. They are produced from tyrosine hydroxylation to DOPA (L-3,4-dihydroxyphenylalanine), with subsequent cell-specific reactions producing dopamine, norepinephrine and epinephrine (Fig. 1). Catecholamines are stored in cytosolic granules and released via a Ca^{2+}-dependent mechanism triggered by the action potential in adrenergic synapses and by sympathetic discharges in the adrenal medulla. Adrenergic receptors are G-protein coupled and comprise α, β and γ subunits. The α-subunit determines the signal transduction pathway, with receptors classified depending upon which α-subunit they contain. G_s and G_i receptors stimulate and inhibit, respectively, the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway, ultimately leading to phosphorylation (G_s) or de-phosphorylation (G_i) of target proteins. G_q receptors stimulate the inositol 1,4,5-triphosphate/diacylglycerol (IP_3/DAG) pathway, ultimately increasing intracellular Ca^{2+} (Fig. 2) [19].

Central nervous system

Neurons located in the locus coeruleus and the lateral tegmental field represent the core of the noradrenergic system. These receive inputs from, and send outputs to, virtually every region of the central nervous system. All adrenoreceptor subtypes are found within the central nervous system, but α_1-receptors predominate. The noradrenergic system is crucial for many physiological (sensory perception and anti-nociception, muscle tone and contraction, modulation of the autonomic nervous system, regulation of body temperature and hormone secretion, sleep–wake cycle) and cognitive (arousal and attention, memory storage and recall, learning and behavioural adaptation) functions. Its alterations are implicated in psychiatric disorders including anxiety, depression and post-traumatic stress [20].

Autonomic nervous system and adrenal medulla

The sympathetic division of the autonomic nervous system originates from the intermediolateral column of the thoracolumbar spinal cord. Axons (preganglionic fibres) leave the spinal cord and enter paravertebral sympathetic ganglia. Here, they stimulate ganglionic neurons, whose axons (postganglionic fibres) form plexuses around the body's main arteries, entering target organs alongside the vascular supply. At the organ level, they release norepinephrine that binds to α- and β-receptors of smooth muscle and glandular epithelial cells, the ultimate target of the autonomic nervous system. The adrenal medulla constitutes the inner portion of the adrenal gland and is an ectopic sympathetic ganglion; indeed, it is innervated by preganglionic fibres from the 7th–9th thoracic segments. In response to sympathetic stimulation, chromaffin cells release epinephrine and norepinephrine into the circulation at a ratio of 85:15 [21].

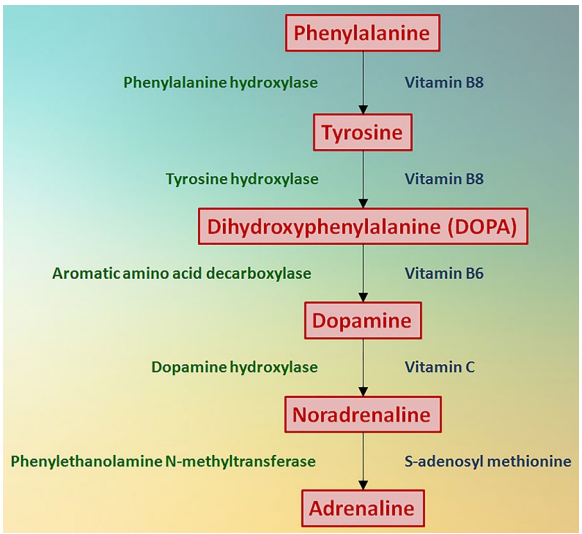

Fig. 1 The catecholamine (*red*) synthesis pathway, with involved enzymes (*green*) and coenzymes/group donors (*blue*). The last biosynthetic step is restricted to some adrenergic neurons and to chromaffin cells in the adrenal medulla, and requires the presence of glucocorticoids (adapted from Wurtman [109])

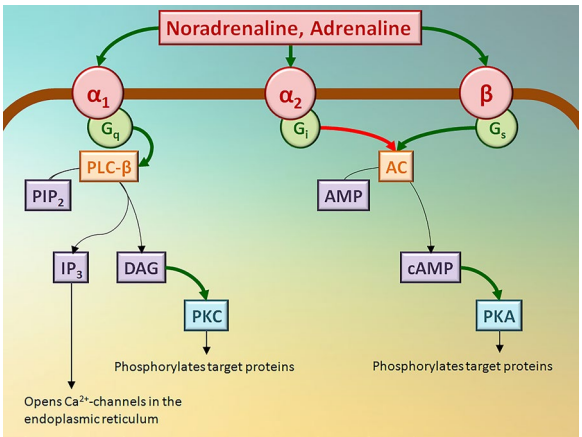

Fig. 2 Catecholamines stimulate α_1-, α_2- and β-adrenoreceptors (*red*), which are coupled with G_q, G_i and G_s proteins (*green*), respectively. Signal transduction pathways are exemplified: effector enzymes are shown in *orange*, second messengers in *purple*, and *green* and *red arrows* indicate stimulation and inhibition, respectively. *PLC-β* phospholipase C-β, *PIP_2* phosphatidylinositol 4,5-bisphosphate, *IP_3* inositol 1,4,5-triphosphate, *DAG* diacylglycerol, *PKC* protein kinase C, *AC* adenylate cyclase, *AMP* adenosine monophosphate, *cAMP* cyclic adenosine monophosphate, *PKA* protein kinase A

Cardiovascular system

Catecholamines increase cardiac output through increasing heart rate and stroke volume via cardiac β_1-receptors, and increasing venous return via venous α_1-receptors. Vascular tone alters through activation of arteriolar constricting α_1-receptors or dilating β_2-receptors. Blood pressure, the product of cardiac output and vascular resistance, changes accordingly.

Chronotropism

Catecholamines modulate heart rate through the sinoatrial and atrioventricular nodes. Stimulation of β_1-receptors on nodal cells leads to phosphorylation of the sodium (Na^+) and Ca^{2+} channels responsible for the inward "funny" current (I_f), leading to an influx of Na^+ and Ca^{2+} and an increased frequency of cell firing.

Inotropism

Activation of cardiomyocyte β_1-receptors increases the amount of Ca^{2+} that enters the cardiomyocyte. Here, Ca^{2+} binds to troponin C, inducing a conformational change in the troponin complex, allowing actin and myosin to bind. A higher Ca^{2+} concentration increases the number of actin–myosin bonds, ultimately increasing the force of heart contraction.

Myocardial energetic requirements

Ca^{2+} entering the cardiomyocyte during each depolarisation must be pumped back outside the cell or into the sarcoplasmic reticulum. As this transport occurs against both electrical and chemical gradients, it requires energy. ATP is also consumed to "re-load" the myosin heads. ATP turnover in cardiomyocytes is extremely high; the heart renews 6 kg of ATP (20 times its own weight) daily. Indeed, cardiomyocytes contain more mitochondria (one-third of their volume) than any other cell type [22]. Catecholamines increase myocardial energy and therefore oxygen requirements as they increase both the amount of ATP required per beat (inotropism) and the number of beats per minute (chronotropism). Catecholamine overload induces cardiomyocyte death in human and animal models, both in vitro and in vivo [23, 24].

Peripheral circulation

As with cardiomyocytes, vascular smooth muscle cell contraction is driven by myosin "loading" and "springing back". In smooth muscle cells myosin activity is regulated by phosphorylation, provided by myosin light-chain kinase (MLCK). Catecholamines induce either vasoconstriction or vasodilation depending on the receptor they bind to, and, ultimately, upon their effect on MLCK. The α_1-adrenoreceptors increase intracellular Ca^{2+} which, in turn, activates MLCK, thereby inducing contraction. The β_2-adrenoreceptors induce production of cAMP, activation of PKA and phosphorylation of MLCK, inducing relaxation. Some vascular beds are relatively insensitive to catecholamines, either because they have fewer adrenoreceptors, or different mechanisms and mediators

prevail locally. These beds can self-regulate blood flow over a wide range of blood pressures (e.g. cerebral and renal circulations), or couple flow to cellular metabolic demands (e.g. cerebral and coronary circulations). However, the hepato-splanchnic, muscular and cutaneous circulations depend on mean arterial pressure and local vascular resistance for their perfusion. The effect of catecholamines on a regional circulation depends on the balance between increased cardiac output and systemic arterial pressure on the one hand and regional arteriolar tone on the other.

Gastrointestinal tract

Catecholamines can affect virtually every cell within the gastrointestinal tract. Neurally released norepinephrine influences the enteric nervous system located within the submucosa and muscularis of the splanchnic organs. This can act independently of autonomic control to finely modulate epithelial, smooth muscular and immune cells [25].

The gut also produces catecholamines. Being in part gut-derived, norepinephrine is highly concentrated within the portal circulation [26]. Kupffer cells and hepatocytes are thus exposed to high catecholamine levels, norepinephrine induces cytokine production by Kupffer cells [27] and hepatocellular dysfunction via α_2-receptors [28]. Catecholamines also modulate blood flow to the gut and are important mediators in diverting blood flow away from the splanchnic district towards other more needy organs such as the brain, heart and skeletal muscle during, for example, exercise.

Metabolism

Catecholamines induce a catabolic state that is integral to the fight-or-flight response. They promote breakdown of glycogen and triglyceride stores to generate glucose, fatty acids and ketone bodies as ready fuel for heart, brain and skeletal muscle. Catecholamines stimulate lactate release from muscle to provide fuel source for varied organs including brain, liver, heart and kidney [29].

Haemostasis

Sympathetic activation affects haemostasis through inducing release of von Willebrand factor and factor VIII (mediated by β-receptors), and by promoting platelet activation, aggregation and secretion (mediated by both α- and β-receptors). This translates into significantly accelerated blood clotting. Catecholamines stimulate the amplification phase of clot formation and stabilisation so, strictly speaking, they are not prothrombotic but rather induce faster thrombus generation. Thrombus generation has been implicated in the pathogenesis of cardiovascular disease and is likely to occur during critical illness; however, the extent of the phenomenon and its clinical relevance have yet to be determined [30].

Immune system

Adrenergic agents influence virtually every aspect of the innate and adaptive immune response. Immune cells are targeted by the nervous system via exposure to circulating catecholamines, but also via sympathetic innervation of lymphoid organs: bone marrow, lymph nodes, thymus and spleen [31]. Almost all immune cells express (mainly β_2-) adrenergic receptors; moreover, they produce considerable amounts of catecholamines, especially when exposed to pathogens [32]. Activation of the sympathetic and parasympathetic nervous systems are, in general, inhibitory on innate immune responses at both systemic and regional levels. On the other hand, peripheral nervous system activation will often amplify local innate immune responses [33]. Catecholamines also modulate proliferation, differentiation and apoptosis of the adaptive immune system cells, as well as cytokine production (see below).

Pathological effects of catecholamines and impact on outcomes

The previous section highlights the crucial role that catecholamines play in health. This can however spil over into harm affecting multiple organ systems. However, among all the pleiotropic actions of catecholamines mentioned above and summarised in Fig. 3, only their cardiovascular effects are routinely monitored and targeted in critically ill patients.

The effects of neural activation on the immune system illustrate the potential negativity of excess catecholamines in critical illness. Severe infection represents an obvious stressful state and the innate immune response relies mainly upon non-specific inflammation and phagocyte recruitment to eliminate pathogens. However, catecholamines inhibit the phagocytic capacity of both neutrophils and macrophages in vitro, and impair the ability of neutrophils to generate a respiratory burst [34]. Overall, the in vitro effect of catecholamines can be summarised as an inhibition of adaptive immunity, characterised by generalised lymphopenia—due to inhibition of proliferation of T helper, T cytotoxic and B cells—and a shift in Th1/Th2 balance towards Th2 polarisation, as demonstrated by low Th1/Th2 cell, TNF-α/IL-4 and IFN-γ/IL-4 ratios [35, 36]. If these effects are translated to the in vivo situation, these would appear to be counter-intuitive in combatting infection. On similar lines, catecholamines can promote growth of virtually every bacterial species [37–39], perhaps through increasing iron availability [40]. In addition, they augment bacterial virulence by promoting biofilm formation and virulence-related gene transcription [41],

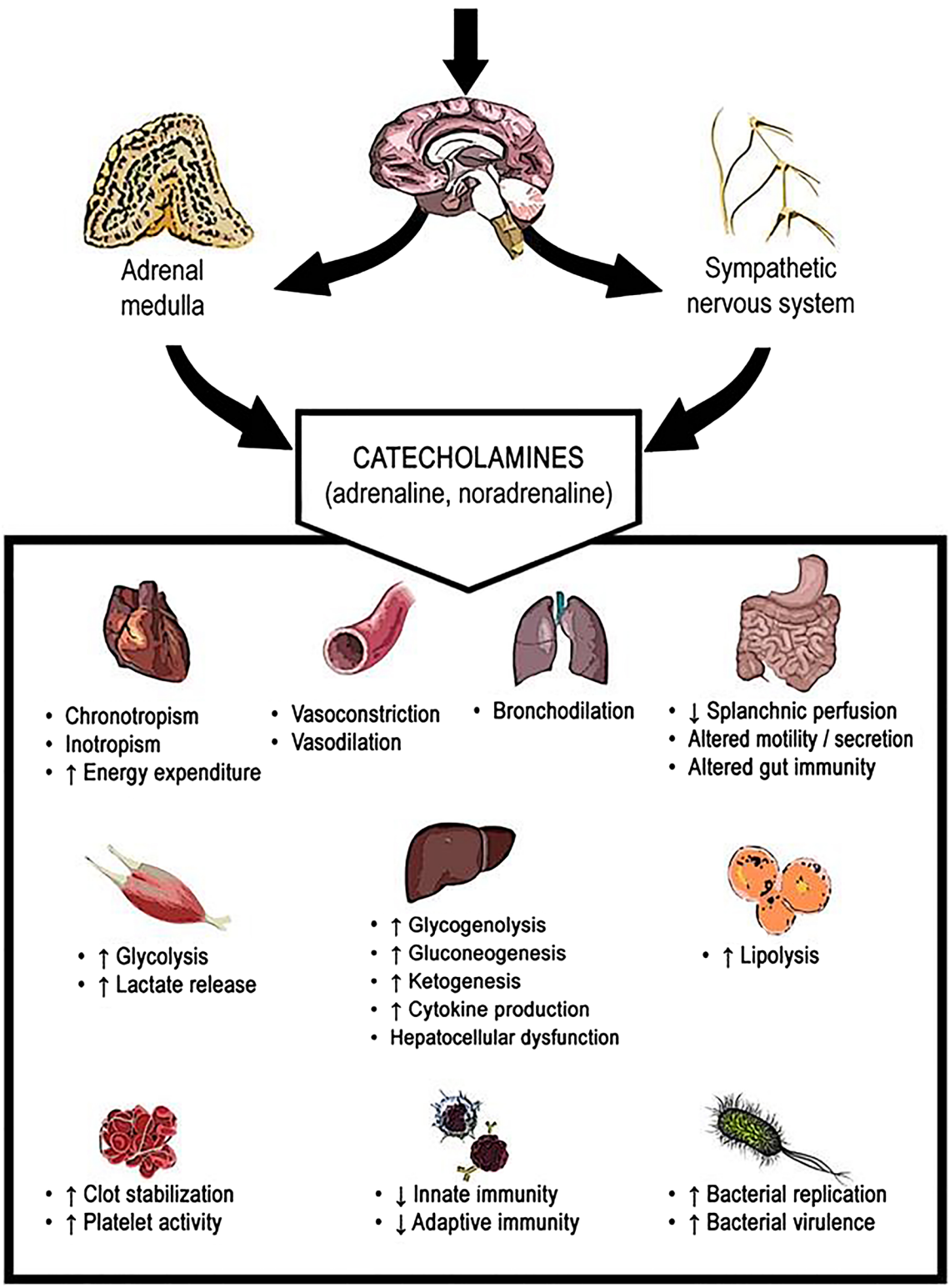

Fig. 3 Pleiotropic effects of neurally released (via the sympathetic nervous system) and circulating (produced by the adrenal medulla) catecholamines

and bacterial recovery following an antibiotic challenge [42]. Catecholamines can mimic bacterial signalling molecules termed "autoinducers" [43]; these operate within the context of bacterial collective decision-making (*quorum sensing*). Depending upon environmental conditions, bacterial behaviour can change from beneficial or neutral (commensal/saprophytic) to organised host attack (pathogenic) [44]. The interplay between the adrenergic and immune systems and bacteria is indeed highly complex. Indeed, a picture of lymphopenia, a low Th1/Th2 ratio and bacterial overproliferation identical to that induced by catecholamines in vitro are found in vivo in both animal models and patients with stroke-associated infections [45, 46]. High catecholamine levels are associated with more severe lymphopenia, and a greater risk of infection and death [46, 47]. In murine models, β-adrenergic blockade could reverse these immunological and microbiological alterations and improve survival [45]. In critically ill patients, lymphopenia and a low Th1/Th2 ratio are poor prognostic biomarkers [48].

With respect to metabolism, excess catecholamines induce insulin resistance, increase hepatic glycogenolysis and gluconeogenesis, and inhibit glycogen synthesis in skeletal muscle, all of which induce hyperglycaemia [49]. This provides a ready source of glucose substrate in acute stress, but is detrimental if prolonged. The β_3-receptors on adipose cells mediate the lipolytic effects of catecholamines by stimulating hormone-sensitive lipase, which breaks down triglycerides to glycerol and fatty acids that are subsequently released into the circulation. Free fatty acids represent an important energy source for the heart; however, their accumulation has both pro-inflammatory [50] and cardiotoxic [51] effects.

The splanchnic circulation is an important vascular bed jeopardised during shock states [52]. Catecholamines, most notably epinephrine, are potent mesenteric vasoconstrictors. While helping to preserve 'vital' organ perfusion, they can induce or aggravate gut ischaemia [53] and perhaps contribute to decreased barrier function, with translocation of bacteria and/or toxins [54]. Circulating catecholamines promote leukocyte influx to the intestinal mucosa [55], bacterial–epithelium adhesion [56], bacterial internalisation [57] and virulence (see above).

A hyperadrenergic state is responsible for the reversible myocardial depression that characterises both phaeochromocytoma crisis [58] and the stress-related (Takotsubo) cardiomyopathy [59]. This latter "broken heart" syndrome can be triggered by a physical or emotional upset and is characterised by very high plasma levels of catecholamines and cardiac injury/dysfunction biomarkers such as troponin and B-type natriuretic peptide, echocardiographic abnormalities such as apical ballooning, and variable electrocardiographic changes yet normal coronary arteries. Stress cardiomyopathy can mimic acute coronary syndromes and may lead to heart failure; it is also recognised after isolated brain injury, perhaps representing the ultimate effort of the damaged brain to ensure its own perfusion at any cost [60].

In many other clinical conditions not primarily caused by an adrenergic surge, a persistent stress response can be identified. In fact, numerous examples can be found where adrenergic excess, both endogenous and exogenous, is associated with poor outcome. Catecholaminergic overload is associated with a poor prognosis in acute coronary syndromes, heart failure, liver cirrhosis and acute cerebrovascular disease [61–64]. High catecholamine levels prognosticate worse outcomes in patients with trauma and infection [65, 66] regardless of disease severity, and even in otherwise healthy, high-functioning elderly subjects [67].

Notwithstanding this association with adverse outcomes, adrenergic agonists remain the mainstay of cardiovascular support. Norepinephrine is the current recommended first-line agent for low vascular resistance states, while dobutamine is recommended for myocardial dysfunction [68]. Epinephrine has both inotropic and pressor properties that can be used as an alternative to either [69]. It is likely that these exogenous catecholamines will add further to the endogenous stress response, therefore increasing total adrenergic stress. After adjustments for propensity scoring, dobutamine administration was independently associated with increased mortality in acute heart failure and after cardiac surgery [70, 71]. High levels of endogenous [72] and exogenous [73] catecholamines as well as a persistently high heart rate [74] predict poor patient outcomes in sepsis. While high catecholamine levels could simply be a marker of disease severity, they may also be a perpetrator of further organ dysfunction. Indeed, increasing catecholamine doses were associated with increasing mortality, independent of effects on blood pressure [75]. Even in the setting of cardiac arrest, epinephrine use and dose are independent predictors of poor recovery [76, 77].

Alternatives to catecholamines

The potential iatrogenic contribution of catecholamine administration to poor outcomes demands further study. While useful and even life-saving for short-term restoration of tissue perfusion or correction of life-threatening hypotension, catecholamines—like any drug—can be poisonous when given in excess. Attempting to minimise catecholamine dosing by selecting an appropriate blood pressure target for the individual patient, optimising sedation and other hypotensive/myocardial depressant agents, optimising fluid loading

and using alternative approaches should all be given due consideration.

The first step towards reducing adrenergic (over)load is to not necessarily target "normal" or "supranormal" haemodynamic values. While too low a blood pressure or cardiac output may compromise tissue perfusion and oxygenation, neither increasing blood pressure >65 mmHg [78] nor targeting "supranormal" values of cardiac output [79] translated into an overall survival benefit. Indeed, previously normotensive patients trended to worse outcomes when a higher blood pressure was targeted [75]. Similarly, many patients with critical illness have often unrecognized diastolic dysfunction and this may be compromised further by the use of catecholamines [9]. In spite of this evidence, catecholamine overuse is still commonplace, even when the mean arterial pressure is well above the declared targets. In a recent randomised controlled trial, most patients had mean arterial pressure values well above the target range, yet were still receiving high dose of catecholamines despite the study protocol prompting their rapid de-escalation [78].

A variety of non-adrenergic inotropes and vasopressors, and adjunct therapies have been investigated for myocardial depression and vasoplegia in both preclinical and clinical studies (Table 1). These agents also have their own side-effect profiles. Thus, none have yet conclusively demonstrated a clear benefit over adrenergic equivalents, and some studies were stopped prematurely because of harm [80, 81]. However, post hoc analyses do suggest benefit in certain subsets of patients. Options for vasoplegia include vasopressin and its analogues, nitric oxide and eicosanoid modulation [82, 83], angiotensin II [84], inhibition of vascular smooth muscle potassium channels [85], and fever control by external cooling [86]. Despite no overall outcome benefit compared to norepinephrine, low dose AVP reduced catecholamine requirements and offered improved survival rates in patients receiving lower doses of norepinephrine at baseline [87]. Myocardial depression has also been treated with levosimendan or glucose–insulin–potassium therapy; preclinical or small patient studies demonstrate short-term benefits [88, 89]. A randomised controlled trial of 516 patients assessing levosimendan in septic shock is shortly to complete enrolment [90]. In terms of adjunct therapy, corticosteroid therapy has been extensively studied in septic shock; corticosteroids increase adrenergic receptor transcription and thus cardiac [91] and vascular [92] responsiveness to catecholamines, and many critically ill patients have adrenal dysfunction which is prognostically relevant [93]. Clinical trials demonstrated that stress-dose glucocorticoids led to a quicker resolution of shock [94]. While there was no overall survival effect, a benefit was seen in patients with vasopressor-resistant shock, for which corticosteroids are currently recommended [68].

Finally, significant attention has been stimulated by a recent single-centre study from Rome [95] assessing the role of beta-adrenergic blockade in a poor prognosis subset of patients with septic shock, i.e. requiring high doses of catecholamines after 24 h and with a concurrent tachycardia. Those patients randomised to esmolol demonstrated significant reductions in mortality, time on vasopressors, and renal and myocardial injury compared to the control group.

The stress response is highly preserved in different species. From an evolutionary point of view, the organism must be able to cope with physically or psychologically demanding situations. However, as critical illness and management in a critical care unit are characterised by a severe and abnormally prolonged stressor response, this response may become maladaptive. Given this premise, attenuation of an excessive adrenergic component of the stress reaction is a tempting therapeutic option during sepsis and other critically ill states. Pretreatment with β-blockers reduced mortality in animal models [96], while β-blocker use before hospital admission was associated with increased survival rates [97, 98]. During established sepsis in animal models, beta blockade controlled heart rate without reducing stroke volume or blood pressure [99]; furthermore, improved cardiac function, decreased inflammation, preserved intestinal barrier function and improved survival have all been demonstrated [96, 100–103]. In patient studies, titration of β-blocker dosing to a target heart rate appears feasible without compromising haemodynamics in most patients; stroke volume usually increases while catecholamine requirements decrease [95, 104]. Possible mechanisms include improved ventricular filling and ventricular-arterial coupling; restoration of adrenergic receptor density, which may have been reduced by excessive catecholamine stimulation [101, 105]; and a decrease in the systemic inflammatory response [106, 107]. More investigation is required to confirm benefit from beta blockade in sepsis and other critical illness states. Patient selection and close monitoring are likely to be crucial in this setting because of the risk of worsening myocardial dysfunction. Fixed-dose (i.e. not titrated to individual needs) beta blockade can be detrimental [108].

Conclusions

Although some degree of sympathetic activation is required for survival of a patient or animal under the stressful conditions of sepsis, adrenergic overload has several underappreciated side effects that may impact negatively on final outcome. Several strategies exist to avoid catecholamine overstimulation during critical illness,

Table 1 Alternatives to catecholamines for inflammatory shock

Drug	Clinical results
Vasopressors	
Vasopressin and analogues	
Vasopressin	Vasopressor, possible survival benefit in less severe patients
Terlipressin	Vasopressor; no major trials
Selepressin	Vasopressor, reduces capillary leak; ongoing clinical trial
Renin–angiotensin–aldosterone system	
Antgiotensin II	Vasopressor; no major trials
Nitric oxide (NO) system inhibitors	
Methylene blue	Vasopressor; no major trials
iNOS inhibitors (L-NMMA)	Vasopressor, but increases mortality
NO scavengers (PHP)	Vasopressor, but increases mortality
Eicosanoid system inhibitors (NSAIDs)	
Nonselective (ibuprofen)	Minor haemodynamic improvement; no effect on outcome
COX-2 inhibitors (lornoxicam)	No haemodynamic improvement; no major trials
ATP-sensitive potassium channel blockers	
Sulfonylureas (glibenclamide)	No haemodynamic improvement, more hypoglycaemia; no major trials
Inotropes	
Phosphodiesterase III inhibitors	
Milrinone	Inodilator; no major trials in sepsis/shock
Na^+/K^+-ATPase inhibitors	
Digoxin	Inotrope in heart failure; no major trials in sepsis/shock
Novel inotropes	
Levosimendan	Inodilator; ongoing clinical trial
Omecamtiv mecarbil	Inotrope in heart failure; no data in sepsis/shock
Istaroxime	Inotrope in heart failure; no data in sepsis/shock
Metabolic enhancement	
High-dose GIK	Haemodynamic improvement; no major trials
Adjunct therapy	
Glucocorticoids	
Low dose	Haemodynamic improvement, possible survival benefit in more severe patients
High dose	Haemodynamic improvement, but increases mortality

Non-adrenergic options for vasoplegia and myocardial depression, as well as steroid adjunct therapy, are summarised. Only drugs that reached the clinical scenario were included

NOS NO synthase, *L-NMMA* L-N^Gmono-methylargininine, *PHP* pyridoxalated haemoglobin polyoxyethylene, *NSAIDs* non-steroidal anti-inflammatory drugs, *COX* cyclooxygenase, *GIK* glucose–insulin–potassium

including acceptance of abnormal haemodynamic values that remain compatible with adequate organ perfusion, use of non-catecholamine vasopressors and inotropes, and β-adrenergic blockade. The last of these is a promising therapeutic tool that requires further investigation in order to identify those subset(s) of patients who may either benefit or be harmed from such an intervention.

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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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