Catecholamine treatment for shock—equally good or bad?

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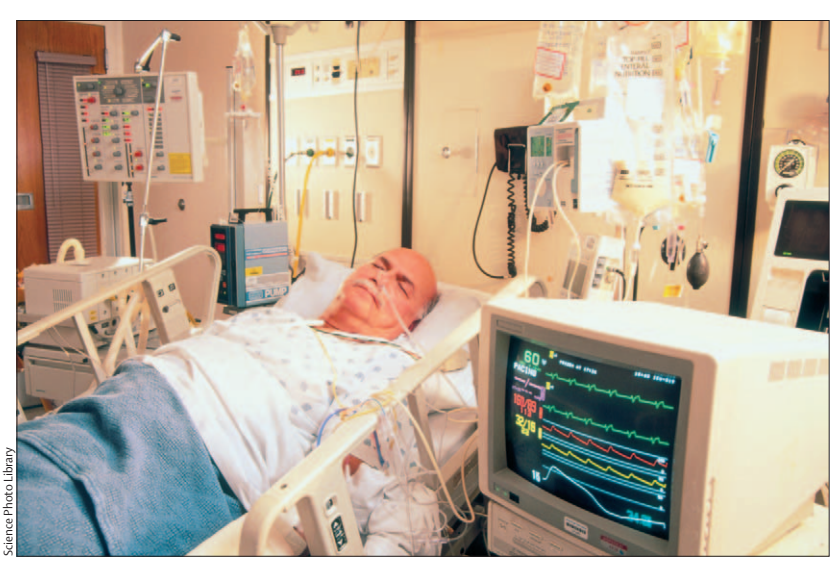
The effectiveness and safety of many interventions in critically ill patients remain poorly validated. Despite heavy promotion by academic advocates, these different strategies often show little to no benefit when tested in randomised multicentre studies. This unfulfilled promise applies to procedures as diverse as albumin versus saline, "renal" dopamine, pulmonary-artery catheterisation, and, more recently, intensive insulin treatment, selective gut decontamination, and corticosteroids for septic shock. Why the efficacy of such treatments achieved in enthusiastic experts' hands often fails to translate into general effectiveness merits further study. Possible explanations include the choice of patient, target or treatment endpoints, protocol compliance, and potential antagonism or synergism with one or more concurrent treatments or procedures unique to some but not other intensive-care units.

To this ever-expanding collection of busted flushes can be added the choice of catecholamine in the treatment of septic shock. Despite studies that highlight the negative effects of epinephrine on splanchnic blood flow, metabolism, and acid-base balance, and an absence of recommendation for its use in adult patients,[1] this catecholamine remains a popular treatment option for septic and cardiogenic shock. In today's *Lancet*, however, Djillali Annane and colleagues[2] report no difference in clinical outcomes or safety in a prospective comparison of norepinephrine with or without dobutamine against epinephrine in patients with septic shock. Arguably, their sample-size computations were based on an over-generous anticipation of outcome benefit, yet the absence of any clear signal after 330 patients is adequate to convince me that the choice of catecholamine is equally good or, perhaps more accurately, equally bad.



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Why the concern? Longstanding familiarity with catecholamines equates harm with well-recognised and clinically obvious complications, such as digital ischaemia and tachyarrhythmias. However, we are not generally aware of other detrimental effects that, through their covert nature, are unlikely to be detected in routine practice but might well be clinically pertinent. Such negative consequences include stimulation of bacterial growth,[3,4] an effect mediated by removal of iron from lactoferrin and transferrin by the catechol moiety and its subsequent acquisition by bacteria.[5] This effect has been shown with epinephrine and norepinephrine, and synthetic agents such as dobutamine. Catecholamines also increase factors related to bacterial virulence and biofilm formation.[3] Furthermore, host resistance to bacteria might be compromised because both catecholamines and dopaminergic agents, such as dopamine, dobutamine, and dopexamine, affect activity and survival of most, if not all, immune-cell populations.[6] For example, epinephrine and norepinephrine decrease the proinflammatory effect of endotoxin, but enhance production of the anti-inflammatory cytokine, interleukin 10.[7,8] This increase in interleukin 10 contributes to an immunosuppressive effect on monocytes and macrophages. Norepinephrine also has a direct inhibitory effect on the energy metabolism of monocytes and macrophages.[9]

Plasma catecholamine concentrations rise up to 20-fold in critical illness.[10] Concentrations returned to normal over 5 days in eventual survivors, but rose still further in non-survivors, many of whom received exogenous catecholamines.[10] Excess adrenergic stimulation induces metabolic derangements, including insulin resistance with consequent hyperglycaemia, and muscle catabolism. Despite increasing whole-body and myocardial energy expenditure, catecholamines also reduce metabolic efficiency by suppressing glucose metabolism and enhancing oxidation of fatty acids. The ATP yield per oxygen atom is 2·83 with free-fatty-acid as substrate, compared with 3·17 with glucose. This decreased efficiency, combined with the increase

in cardiac work induced by adrenergic stimulation and peripheral vasoconstriction, will place an excess strain on the failing heart. This effect might be relevant not only for ischaemic myocardial injury[11,12] but also for sepsis, in which myocardial depression is well recognised.[13] Indeed, randomised studies of β-adrenergic agonists or phosphodiesterase inhibitors in decompensated heart failure show worse outcomes than do placebo or inotropic agents that do not increase cAMP, whereas β-adrenergic blockade has been shown to be beneficial in burn injury, heart failure, major surgery, and experimental sepsis.[14]

We are, therefore, stuck between the Scylla of compromised tissue perfusion in septic shock and the Charybdis of the complications of currently recommended first-line treatment.[1] Better alternatives to catecholamines are needed, which might include agents as diverse as vasopressin, levosimendan, or specific inducible inhibitors of nitric oxide synthase. We also need to better define the lowest acceptable blood pressure in individual patients to minimise the harmful effects of excessive catecholamine dosing. Additionally, we should limit the use of concurrent medications that contribute to hypotension (eg, excess sedative dosing) and vascular hyporeactivity (eg, etomidate).

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I have served on advisory boards for Abbott/Orion (levosimendan) and Ferring (vasopressin analogues).

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Speaking out about human rights and health in West Papua

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The recent Human Rights Watch (HRW) report, *Out of Sight*, alerted the international community to the hidden human-rights abuses in West Papua, Indonesia's most easterly province.[1] The effect of the crisis on the health and wellbeing of the indigenous population of West Papua is an issue that has attracted little attention in contemporary medical publications.

West Papua occupies half of the island of New Guinea. Most of its 2 million indigenous inhabitants live in remote villages scattered across the mountainous and forested territory. In 1969, after a referendum brokered by the UN, Indonesia annexed West Papua following a decision-making process that was widely regarded as flawed.[2] Since then, independence groups have waged a low-level guerrilla war against Indonesian rule.

Both restrictions on data gathering by foreigners and the inaccessible terrain create major obstacles to undertaking research in West Papua. The HRW report therefore is invaluable because it provides documentation of systematic abuses, including torture, rape, and extrajudicial killings directed against militants and the civilian population. Police and military personnel who are accused of violations seem to be immune from prosecution.[1] Refugees fleeing persecution have sought asylum in Papua New Guinea and in developed countries, such as the UK and Australia. A participant in our