CRITICAL CARE

COMMENTARY

Another nail in the hammer's coffin?

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Abstract

Blood pressure saggy? Cardiac output low? Oliguria? Increasing acidosis? Peripheries a bit cool? Poor cardiac history? No problem. Just start some dobutamine and watch the numbers improve. And if the patient happens to die, that is their fault. Or is it? Catecholamines are long-established drugs that have never undergone formal testing of long-term outcomes and safety. Their use requires re-evaluation in the light of a wide range of deleterious actions and retrospective studies suggesting harm.

In a carefully performed retrospective study of 1,314 patients undergoing cardiac surgery, Shahin and colleagues found that postoperative use of dobutamine was independently associated with a 2.3-fold increase in mortality and a 2.7-fold increased risk of renal dysfunction, after correcting for preoperative risk, cardiac function, intraoperative management and complications, and cardiac index [1]. A parallel greedy matching propensity analysis in 123 inotrope-exposed patients and 123 unexposed patients confirmed these findings [1]. This study builds upon that previously reported by Fellahi and colleagues in 657 cardiac surgical patients [2].

The decision to start an inotrope after cardiac surgery is often based on physician whim [3] and there is a general nonappreciation of harm. For many years we have displayed a blind devotion to catecholamines, aware but accepting of the occasional problems of tachycardia, arrhythmia and dusky digits. Like furosemide, oxygen, aspirin, digoxin and other familiar friends, catecholamines and phosphodiesterase inhibitors became established before formal long-term outcomes testing of drugs became mandatory, so proof of benefit and safety profiles were never properly characterised. The treatment provided what was claimed on the package insert (an inotropic action) and we looked no further.

Dobutamine was key to Shoemaker and colleagues' concept of supranormal circulatory optimisation of high-risk surgical patients [4], and, to be fair, was an integral part of a successful optimisation protocol after cardiac surgery that targeted mixed venous oxygen saturation and lactate [5]. A perioperative goal-driven approach may thus be more efficacious – and safer – than empiric administration, but this should not be freely extrapolated to other conditions. For example, the Shoemaker approach was forcefully marketed towards managing established severe sepsis and shock, yet, when formally challenged, its use proved deleterious in a dose-dependent manner [6]. While this deterred intensivists from using high doses to achieve targeted values of oxygen delivery and consumption, the general use of catecholamines remains unabated.

A further fillip came from Rivers and colleagues' Early Goal-Directed Therapy strategy for patients presenting with severe sepsis [7]; this study led to dobutamine becoming enshrined in the Surviving Sepsis Campaign guidelines [8], albeit based on a mere 18 patients whose outcomes remain unknown. Recent studies in shocked patients showed equivalent mortality rates when randomised to epinephrine or norepinephrine plus dobutamine [9,10]. But are these equally good or equally bad? A wealth of animal and cell studies show a wide range of covert harm from catecholamines; for instance, stimulation of bacterial growth yet concurrent immunosuppression, decreased metabolic efficiency, potent thrombogenicity, tissue hypoxia through excessive microvascular vasoconstriction, and myocardial damage [11]. A retrospective analysis of catecholamine use in a septic shock trial revealed increased dose-related mortality with progressive increases in blood pressure [12].

What options do we have? Currently, these options are relatively limited and further extensive study is required before any can be strongly endorsed. Phosphodiesterase inhibitors, like catecholamines, have similar detrimental outcomes, and this appears to be a class effect [13,14]. Vasopressin or synthetic analogues such as terlipressin may be potentially superior vasopressors, while levosimendan offers a viable alternative in low cardiac output

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states by increasing contractility through a variety of mechanisms including increased cardiomyocyte calcium sensitisation and peripheral vasodilatation, although not at the expense of a large increase in cardiac work.

New agents in development such as myosin activators and the Na^+/K^+-ATPase antagonists show promise, as does the concept of metabolic modulation – encouraging the mitochondria to use glucose preferentially over fatty acid, thereby generating ATP more efficiently in terms of oxygen consumption [15]. This modulation can be achieved by blocking fatty acid entry into mitochondria (for example, using a carnitine palmitoyl transferase inhibitor such as perhexiline) or by enhancing utilisation of glucose through a high-dose glucose–insulin–potassium infusion. This strategy has become the treatment of choice for life-threatening overdoses of calcium channel blockers and some antidepressants. While an immediate, end-of-the-needle effect is not seen, the treatment still merits exploration in other critically ill patient groups.

In the short term, we can also focus on catecholamine sparing. What blood pressure should we aim for in an individual patient? Guidelines target populations not individuals. If perfusion appears adequate at a mean of, say, 55 to 60 mmHg, is there any point in driving it higher? Furthermore, does the patient need heavy sedation, a frequent side effect of which is hypotension? The crucial recognition of iatrogenic harm through blood transfusion, high tidal volumes, excess sedation, and so forth, can (and should) be readily extended to catecholamine use.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements
The present work was undertaken at University College London Hospitals/University College London, which receives a proportion of its funding from the funding scheme of the UK Department of Health's National Institute for Health Research Biomedical Research Centre.

Published: 8 August 2011

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doi:10.1186/cc10311
Cite this article as: Singer M, Brealey D: **Another nail in the hammer's coffin?** *Critical Care* 2011, **15:**179.