

Beta-blockers in sepsis; time to reconsider current constraints?

New insights into the mechanisms of action of beta-blockers, and the potential consequences for clinical practice, are continually evolving. Originally, this class of drugs were targeted towards treatment or prevention of hypertension, arrhythmias and myocardial ischaemia. Their therapeutic potential then expanded towards the reduction of mortality after myocardial infarction and heart failure.¹ Although these indications are now widely accepted, they were not immediately apparent. So why may the use of beta-blockers be beneficial in patients already suffering from impaired myocardial contractility? Clinical observations suggested that the beneficial effect of beta-blockers was greater in patients with the worst cardiac performance. Concurrent findings that chronic use of an oral beta-agonist was associated with increased mortality^{2,3} led to the re-evaluation of the paradigm, fuelled new research that unravelled the concept of maladaptive sympathetic overstimulation in heart failure,⁴ and changed clinical practice towards the use of beta-blockade.

In parallel to these evolving indications in cardiovascular disease, the role of beta-blockers in sepsis was also being explored. The classical concept of sepsis and septic shock described an overproduction of nitric oxide (NO), leading to an inability to adequately maintain vasomotor tone and hyporeactivity to both endogenous and pharmacologic catecholamines.⁵ In addition to NO, pathogen-associated molecular patterns, damage-associated molecular patterns (including histones), cytokines all contribute to the development of sepsis-induced myocardial dysfunction.⁶ In general, the first line of treatment for these life-threatening symptoms is a combination of alpha- ± beta-agonists, most commonly noradrenaline and dobutamine. Within this context there seems to be no indication for beta-blockers; indeed, they were traditionally contraindicated. However, this view was challenged by several observations. Retrospective data suggested an independent association between the number, duration and dose of alpha- and beta-agonists and mortality in sepsis.^{7,8} Such data are however always hampered by the bias of indication: the sicker the patient, the more the

drug will be administered. Statistical adjustments by multivariate analysis or propensity scoring models help to overcome this problem to some extent, but such design clearly cannot provide definitive answers. Despite these limitations the increased odds of dying within 90 days after a septic insult are reported to be as high as 2.3 in patients with dobutamine, in comparison to well-matched patients without dobutamine.⁸ Epidemiologic data also hinted towards the same direction.

Analogous to statins, a significant reduction in 30-day mortality was observed in a large cohort of mixed ICU patients (including those with sepsis) who were taking beta-blockers prior to ICU admission.⁹ A recent randomized controlled trial found that use of the short-acting beta-blocker, esmolol in a high-risk cohort of septic shock patients was not only associated with a significant reduction in mortality, but also with better cardiac performance.¹⁰

In this issue of the British Journal of Anaesthesia Fuchs and co-workers add another perspective to the already shifting paradigm. In a retrospective analysis they investigated the potential influence of cessation of pre-existing use of beta-blockers in the course of a sepsis-related ICU admission.¹¹ Using multivariate analysis they observed an independent association between discontinuation of beta-blockers and 90-day mortality in a cohort of 296 patients with sepsis or septic shock. The odds of dying within 90 days was 0.57 (confidence interval 0.39-0.83) for those who remained on beta-blockers, in comparison to patients in whom the use of beta-blockers was stopped in the acute phase of their sepsis treatment, suggesting a substantial effect. These data are in line with the BASEL-II-ICU study where a protective effect of the continuation of pre-existing use of beta-blockers on short and long-term mortality was observed. In ICU patients admitted for acute respiratory failure in whom the pre-existing using of beta-blockers was continued at discharge, the 1-year mortality was 16% versus 46% for patients discharged from hospital without a beta-blocker. This was independent of either a cardiac or non-cardiac origin of the respiratory failure.

There are several potential mechanisms underlying the observed 'protective' effects of beta-blockers in the course of sepsis, both cardiac and non-cardiac. The design of the study does not allow conclusions to be drawn beyond an association. It is conceivable that (dis)continuation of beta-blockers is a marker of severity of illness. Statistical 'correction' by multivariate analysis can mitigate this effect to some extent, but does not rule out unknown biases. An alternative explanation is that beta-blockers protect against ischemic heart disease, not uncommonly present in sepsis patients as a pre-existing co-morbidity. However, previous studies suggest the protective effect of beta-blockers was not restricted to patients with pre-existing cardiovascular disease.^{9,11} Due to high levels of endogenous and exogenous catecholamines there is a high likelihood of sympathetic overstimulation in sepsis, with a typical persistence of tachycardia despite adequate fluid resuscitation. This may lead to diastolic dysfunction, the predominant phenotype in sepsis-related myocardial dysfunction, and classically an indication for beta-blockers. Morelli et al showed a substantial improvement in stroke volume with esmolol. This may not only be explained by heart rate reduction allowing better diastolic filling, but also by attenuation of catecholamine-induced cardiomyocyte toxic effects, characterized by inflammation, oxidative stress and abnormal intracellular calcium trafficking, leading to stunning, apoptosis and even necrosis.^{12,13} Adverse effects of catecholamine toxicity may also affect organs other than the heart. Examples include pulmonary oedema, gut ischemia, hypercoagulability, immunomodulation and stimulation of bacterial growth, impaired glucose tolerance, muscle wasting and hyperlactatemia.¹⁴ Finally, the results by Fuchs et al potentially indicate the prevention of the beta-blocker withdrawal syndrome, provoked by a mild and transient hypersensitivity of cardiac beta-adrenergic receptors.¹⁵ Symptoms include tachycardia, sweating, tremors, headaches and angina pectoris. Acute interruption in the use of beta-blockers under conditions other than sepsis, such as pre-existing heart failure, are associated with an attributable risk of death.¹⁶

How should these observations be translated into clinical practice? Further research is needed to confirm any benefit of continuation of beta blockers in a prospective multicentre study, and to clarify

potential differences between the various subtypes of beta-blockers. In the meantime, evidence suggests that it may be worthwhile to maintain use of beta-blockers in patients who are on long term beta-blocker therapy prior to the septic period. This challenges current dogma where continuation of beta-blockers is generally viewed as an unnecessary risk or even contraindicated, especially when there is marked cardiovascular instability. Changing behaviour may be more difficult than anticipated; despite well-accepted indications for beta-blockers, additional strategies are often needed to assure compliance.¹⁷

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