Perioperative beta-blockade: beyond myocardial ischaemia

Although perioperative beta-blockade is recommended for patients at higher risk of myocardial ischaemia (Eagle et al, 2002), adoption of such guidelines is limited. Concerns over clinical trial data, plus the safety of perioperative beta-blockade, persist. Since preoperative revascularization does not reduce mortality, a very large, increasingly elderly patient population will present major challenges for the anaesthetist.

Mangano et al (1996) suggested that perioperative beta-blockade with atenolol reduced mortality in patients up to 2 years post-major non-cardiac surgery. However, this trial had several important limitations. First, patients were randomized to beta-blockade regardless of whether they were already routinely on beta-blockers; withdrawal is associated with a high incidence of myocardial ischaemia.

Second, outcomes in the treatment *vs* control groups were only compared from the period of beta-blockade. If the period of beta-blockade was included in the analysis, no differences occurred between the groups. Limited risk stratification, heterogeneous surgical procedures and different analgesic modes also complicate interpretation of these data.

The carefully conducted study by Poldermans et al (1999) presents another issue, namely generalizability. Dobutamine echocardiography identified 102 vascular surgical patients with reversible myocardial ischaemia, having screened 1351. Patients were then randomized to bisoprolol or standard of care. Mortality in patients randomized to bisoprolol was 3.4% *vs* 34% in the standard of care group. Because this was a high-risk group, extrapolating these data to other patient groups is difficult.

This is highlighted by a recent propensity score analysis, suggesting that beta-blockers are associated with excess mortality in patients at lowest preoperative cardiac risk (Lindenauer et al, 2005). Although heart rate control appears to be important, presumably through reduction of myocardial oxygen consumption, resting heart rate alone is an imprecise marker of adequate beta-blockade. Indeed, the dose required to achieve pharmacologically-driven increases in heart rate by 25 beats/min is similar regardless of previous beta-blockade, possibly as a result of beta receptor upregulation.

In support of this, a meta-analysis by Devereaux et al (2005) concluded that chronic use of beta-blockade does not seem to confer protection. However, the consistent observation that surprisingly small differences in heart rate (~10 beats/minute) occur between control and treatment study groups (even in the Poldermans study) raises the possibility that extracardiac, non-heart rate limiting effects are also advantageous in the perioperative period. This idea is supported by the association between reduced perioperative mortality and beta-blockade in patients with at least two preoperative risk factors – even though these factors may not necessarily include overt ischaemic heart disease (Lindenauer et al, 2005).

How could beta-blockade confer protection?

In addition to the major effects of beta-blockade in reducing heart rate (increasing diastolic perfusion time) and improving contractility (reducing oxygen demand), several other plausible but largely unexplored properties may improve perioperative outcome:

- Beta-blockers have potent anti-arrhythmic effects, enhancing atrial rate control particularly during acute ischaemia and cardiac surgery
- Attenuation of excessive beta-adrenergic stimulation in heart failure restores myocardial adrenoceptor sensitivity
- Immunological effects of acute and chronic sympatholysis are unclear. While acute adrenergic activation may dampen inflammation, experimental data suggest that prolonged increases in sympathetic drive could result in immunoparesis
- Beta-blockers differ substantially in their pharmacological and pharmacokinetic properties.

Conclusions

If perioperative beta-blockade in the wider surgical population is beneficial, several mechanisms are likely to contribute. Although ongoing Canadian (POISE) and European (DECREASE-IV) clinical trials focus on myocardial ischaemia, these data may also give further clues as to whether the benefits of beta-blockade may be attributable to other mechanisms, including extracardiac actions. BJHM

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