Perioperative beta-blockade: does it improve outcome?

The use of beta-blockers in the management of patients with coronary artery disease, arterial hypertension and cardiac failure suggests that they should offer significant protection against perioperative cardiac events. Initiating or continuing beta-blockade in patients presenting for surgery may be regarded as offering protection with no need for further assessment of investigations. However, data do not support this and appropriate investigations are needed.

In 1997, the American College of Physicians published a guideline for assessing and managing the perioperative risk of coronary artery disease associated with major non-cardiac surgery. An important conclusion was that all eligible patients should receive a beta-blocker (Palda and Detsky, 1997).

Such a conclusion was not surprising because a large proportion of the complications of anaesthesia and surgery results from coronary events (Mangano, 1995) and beta-blockers are very effective in the management of angina and myocardial infarction. They reduce the mortality of myocardial infarction (Anon, 1986) and protect against the risk of reinfarction; the mortality reduction can be as high as 36% (Owen, 1998).

In the UK, 60% of the 20 000 patients who die within 30 days of surgery have evidence of coronary heart disease (Callum et al, 2002) and the number of cardiac death is approximately 9000 per annum (Callum et al, 1999). In addition to cardiac deaths, there are many cardiac complications. Their number can be estimated at between 90 000 and 180 000 per annum. This is in keeping with observations in the US (Mangano, 1995).

The major cardiac complications of anaesthesia and surgery include myocardial infarction, unstable angina, life-threatening arrhythmias, and acute left ventricular failure. Postoperative myocardial infarction occurs in between 2.5% of unselected patients aged over 40 years and 8.6% of patients in whom suspicion of coronary artery disease is sufficiently strong to justify myocardial perfusion scintigraphy (Mangano, 1998). In patients with confirmed significant coronary artery disease on dobutamine-sensitized echocardiography, or myocardial perfusion scintigraphy, vascular surgery may be associated with a 30% risk of myocardial infarction or cardiac death (Poldermans et al, 1999; Mamode et al, 2001).

In the face of such a major health risk, active steps must be taken to protect patients as these complications, devastating as they are in the short-term, significantly impair the long-term prognosis of the sufferers (Mangano et al, 1992). In addition, the cost of such complications is considerable; approximately £1500 for the treatment of the acute phase of each complication (Department of Health, 2005), a potential annual cost of £135 million and £270 million.

Professor Pierre Foëx *is Professor of Anaesthetics in the Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU*

Identification of high-risk patients

Identifying high-risk patients can be difficult because the medical history may be unrevealing and obvious clinical manifestations of coronary artery disease may be absent. The electrocardiogram can also be normal at rest. Many patients with coronary artery lesions are asymptomatic as their ischaemia is silent. Myocardial infarction can also be totally or almost totally silent, especially in patients with diabetes.

While coronary angiography is the gold standard for the evaluation of coronary heart disease, it is impractical to carry it out in all patients presenting for major non-cardiac surgery who are at risk for coronary artery disease because of costs and risks. Non-invasive screening tests are useful; they are based on the imposition of a physical or pharmacological challenge (dobutamine, dipyridamole or adenosine) used together with electrocardiography, echocardiography, radionuclide angiography (MUGA scan), or myocardial scintigraphy (thallium, technetium-99m sestamibi). The stress is used to elicit reversible ischaemia (ST segment depression, reduced ejection fraction, new wall motion abnormalities, reversible defect of thallium or technetium-99m sestamibi uptake). Reversible ischaemia indicates the presence of significant coronary artery lesions.

Coronary revascularization or beta-blockade?

In the presence of significant coronary lesions should coronary revascularization be offered or medical treatment?

If the coronary lesions or symptoms constitute a clear indication for coronary revascularization in their own right, independently from impending non-cardiac surgery, revascularization should precede a non-cardiac operation (Eagle et al, 2002). By contrast, prophylactic coronary revascularization should be limited to patients with significant coronary disease undergoing high-risk major

surgery, as stated in the American College of Cardiology and American Heart Association (ACC/AHA) guideline (Eagle et al, 2002).

This approach has been called into question because a prospective study has shown no benefit of coronary revascularization (coronary bypass surgery or angioplasty) before vascular surgery (McFalls et al, 2004). However, patients with severe coronary disease (main left coronary artery) or severe cardiac failure were excluded. It is evident that a full cardiological evaluation had been carried out in these patients. Moreover, all patients were on maximum medication including beta-blockers (85%), statins (55%) and antiplatelet drugs (70%). This study, however, does not prove that revascularization is ineffective in all patients as they had been carefully evaluated and selected.

In the face of some uncertainties regarding coronary revascularization, an alternative approach is to consider that all eligible patients with risk factors for coronary artery disease should be treated with beta-blockers during the perioperative period and beyond (Grayburn and Hillis, 2003).

Role of beta-blockers

Beta-blockers reduce myocardial oxygen demand, decrease the effects on the heart of perioperative sympathetic overactivity, may reduce overall sympathetic activity, redistribute coronary blood flow towards compromised areas, and modulate dysregulated cytokines (Ohtsuka et al, 2001). As there is increasing emphasis on the role of inflammatory mediators in the development of unstable coronary syndromes (Vallance et al, 1997), this may contribute to their efficacy.

Medical patients

Beta-blockade reduces mortality of myocardial infarction (Anon, 1986) and protects against the risk of re-infarction, with a mortality reduction as high as 36% (Owen, 1998). Beta-blockers reduce the incidence of silent ischaemia in ambulatory patients; this is accompanied by a significant reduction of the relative risk of cardiac events (Pepine et al, 1994).

Beta-blockers play an important role in the management of arterial hypertension and can be used as a first-line treatment. However, a systematic review by Carlberg et al (2004) and the interruption of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (2005) cast doubt on the efficacy of atenolol in the management of hypertension.

Surgical patients

Acute beta-blockade

For over 30 years, acute beta-blockade has been shown to reduce the risk of perioperative myocardial ischaemia and ventricular arrhythmias (Prys-Robert et al, 1973; Stone et al, 1988a; Wallace et al, 1998). In 1987, Pasternack et al were able to show that beta-blockade decreased the risk of perioperative myocardial infarction and arrhythmias. This was confirmed by Yeager et al (1995) in a case control study. Benefits were also shown in other studies.

The American College of Physicians guideline recommending the use of beta-blockers (Palda and Detsky, 1997) was published shortly after a randomized study by Mangano et al (1996). This study included 200 patients with, or at risk of, coronary artery disease who were randomly allocated to receive atenolol 100 mg or a placebo for 7 days starting the day of surgery. Although there was no difference in respect of immediate perioperative mortality or myocardial infarction, event-free survival up to 2 years was significantly better (91%) in beta-blocked patients than in the placebo group (81%). While these results appeared very convincing, the study was later criticized because beta-blockade was stopped in some patients before randomization, there were more patients with diabetes in the placebo group, and the in-hospital events were not included in the analysis.

In 1999, Poldermans et al published a study of patients undergoing vascular surgery in whom severe coronary artery disease was demonstrated by the presence of reversible ischaemia on dobutamine-sensitized echocardiography. Treatment with bisoprolol started at least 1 week before surgery and continued for 30 days after surgery. The authors reported lower 30-day perioperative mortality (3.4% *vs* 17%) and reduced incidence of myocardial infarction (0% *vs* 17%) in patients treated with the beta-blocker. Favourable effects were also observed over a 2-year follow-up period (Poldermans et al, 2001). However, the benefits of beta-blockade demonstrated in this study cannot be extrapolated to all patients with risk factors for coronary artery disease because treatment was given to patients in a very high-risk category. Indeed, from an initial group of more than 1350 patients with one or two risk factors for coronary artery disease, over 800 underwent dobutamine-sensitized echocardiography before vascular surgery and only 173 patients satisfied the selection criteria. The 100% reduction of the risk on perioperative myocardial infarction is a surprising finding as most studies of beta-blockade in myocardial infarction show a risk reduction ranging between 16 and 36% (Owen, 1998).

Beta-blockade seems to be a logical answer to the prevention of cardiac complications of anaesthesia and surgery in patients with risk factors for, or with, coronary heart disease. Indeed, as early as 1988, an editorial in *Anesthesiology* was entitled 'Should we all have a sympathectomy at birth, or at least preoperatively? (Roizen, 1998). However, there are few randomized studies of the efficacy of perioperative beta-blockade and in several of them the differences fail to reach statistical significance.

The meta-analysis by Stevens et al (2003) showed benefits of beta-blockade but relies for statistical significance

on the study of Poldermans (1999). Without it the benefits are not statistically significant (Devereaux et al, 2004).

As a result of limited evidence, the latest ACC/AHA guideline (Eagle et al, 2002) states that:

> **'appropriately administered beta-blockers may reduce the risk of myocardial infarction and death in high risk patients. Where possible beta-blockers should be started days or weeks before elective surgery, with doses titrated to achieve a resting heart rate between 50–60 beats per minute.'**

The latter statement echoes the major importance of heart rate control in the prevention of myocardial ischaemia (Raby et al, 1999).

Chronic beta-blockade

Surprisingly, evidence for perioperative protection by chronic beta-blockade is lacking except in coronary bypass surgery (ten Broecke et al, 2003). In non-cardiac surgery, the incidence of perioperative silent myocardial ischaemia is not reduced in patients on long-term beta-blockers (Sear et al, 2001).

A meta-analysis of observational studies has failed to demonstrate any protection (Giles et al, 2004). This may reflect the presence of more severe coronary disease in patients on chronic beta-blockers, beta-receptor up-regulation (Yndgaard et al, 1997), increased number and sensitivity of $beta_2$-adrenoceptors when selective $beta_1$-blockers are used, or simply inadequate beta-blockade. It is also known that the heart rate at which ischaemia develops is lower in chronically beta-blocked patients (Tzivoni et al, 1998). Therefore, relatively small, apparently innocuous, increases in heart rate during the perioperative period could cause ischaemia in chronically beta-blocked patients, negating the beneficial effects of these agents. Protection cannot, therefore, be implied because of chronic beta-blockade. Vigilance is essential.

KEY POINTS

- Cardiac complications of anaesthesia and surgery are frequent and result, mostly, from coronary artery disease.
- Perioperative cardiac complications have short- and long-term consequences.
- Identification of high-risk patients often requires non-invasive or invasive investigations of the coronary circulation and may lead to selective coronary revascularization.
- Beta-blockade is likely to offer some protection in moderate- to high-risk patients but its efficacy in all patients at risk for, or with coronary disease, has not been demonstrated unequivocally.
- Chronic beta-blockade does not seem to offer protection.
- Full evaluation and pharmacological prophylaxis using beta-blockers and other drugs such as statins may offer better protection than beta-blockade alone.

While acute beta-blockade appears to be legitimate, it is important to stress that it may not be without some hazards. When given as premedication, beta-blockers were found to decrease the incidence of myocardial ischaemia. However, some patients developed hypotension (Stone et al, 1988b). Several recent studies were carried out in patients admitted to high dependency or intensive care units. In such environments adverse effects, if any, could be easily detected and corrected. This may not be the case if patients are admitted to an ordinary ward. Therefore, the safety of introducing perioperative beta-blockade when patients are on the ward needs to be demonstrated.

It is well known that beta-blockade should not be initiated in patients with obstructive lung disease or conduction disorders. Although beta-blockers are now part of the treatment of cardiac failure, their introduction immediately before surgery in patients with poor left ventricular function is contraindicated. If they are used caution is essential as, in patients with cardiac failure, beta-blockade always starts with very low doses and titration takes several weeks (Gottlieb et al, 2002).

While a more widespread use of beta-blockers perioperatively may be justified, their administration may be made safer by starting treatment at least a week or more before surgery (Eagle et al, 2002), and by increasing the extent of monitoring of blood pressure and heart rate during the postoperative period, with clear protocols for their omission should hypotension or bradycardia develop. If this can be achieved, beta-blockers could probably be used in more patients, thereby reducing the risk of cardiac complications of anaesthesia and surgery.

Hopefully a definitive answer will be given by the POISE (PeriOperative ISchemic Evaluation) study, a randomized study of 10 000 patients with coronary heart disease or risk factors who will receive a controlled release preparation of metoprolol or a placebo (Devereaux et al, 2004). Over 3000 patients have been enrolled to date.

Conclusions

The uncertainties in respect of beta-blockade indicate that consideration should be given to other cardiovascular drugs such as nitrates, calcium channel blockers, alpha2-adrenoreceptor agonists, potassium adenosine triphosphate-dependent channel openers, sodium/hydrogen blocking agents (cariporide) or angiotensin-converting enzyme inhibitors. Unfortunately, the efficacy of most drugs is either lacking or is limited (Stevens et al, 2003). It may be that most drugs have limited efficacy because they do not influence the release and/or the effects of inflammatory mediators. By contrast, several recent publications have shown that statins protect surgical patients against cardiac complications of anaesthesia and surgery with significant risk reduction of the order of 30% (Kertai et al, 2004; Durazzo et al, 2004; Lindenauer et al, 2004; O'Neil et al, 2005).

As the efficacy of beta-blockade and other drugs is relatively limited, it remains essential to identify high-risk patients. This often requires testing their coronary reserve by an exercise- or dobutamine-sensitized test such as echocardiography, radionuclide angiography or myocardial scintigraphy. This is the best way of making a decision about the patient's management including coronary revascularization, prophylactic drug therapy and properly informed consent. **BJHM**

Conflict of interest: Professor Foëx is an investigator in the POISE study.

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