Is there still a place for beta-blockers in perioperative cardioprotection?

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Cardiovascular complications, such as hypertension or hypotension, myocardial infarction, left ventricular failure with pulmonary oedema, arrhythmias or stroke, comprise a substantial part of postoperative complications. It is estimated that they can occur approximately in one of ten patients (1). Not only they prolong the length of stay in hospital and increase costs of treatment but also have an adverse impact on quality of life and long-term prognosis, shorten life expectancy and in the worst case can end fatally. Therefore, all possible approaches to risk reduction are warranted.

These approaches also include **perioperative beta-blocker administration**, which has even been listed as one of quality of care measures recommended by National Quality Forum, an organization evaluating a quality of delivered health care in USA (2). However, new information has recently emerged. This casts doubt on the safety and efficacy of routine beta-blocker administration to almost all patients at risk of cardiac events in the perioperative period.

Pathophysiologically, beta-blocker therapy is based on studies showing their beneficial effects in patients after myocardial infarction or with heart failure, in which they reduce mortality and morbidity and improve quality of life (3,4). Beta-blockers decrease myocardial oxygen demand by their negative inotropic and chronotropic effects and can thus prevent exceeding ischemic threshold. Because hypertension and tachycardia are undoubtedly

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involved in postoperative ischemic complications it is logical to use in these drugs in the perioperative period, too.

Beta-blocker administration in the perioperative period is based mainly on results of two randomized controlled trials performed in 1990's. Mangano et al. compared effects of atenolol or placebo on overall survival and cardiovascular morbidity in 200 patients with or at risk of coronary artery disease undergoing elective non-cardiac surgery in general anesthesia. In the atenolol group they demonstrated a reduction of overall mortality by 55% and an increase of event-free survival throughout the two-year study period by 15% (5). In the second fundamental study using preoperative stress echocardiography Poldermans et al. looked at the benefit of perioperative bisoprolol in 112 patients with new regional wall motion abnormalities induced by dobutamine in 1-4 left ventricular segments undergoing vascular surgical procedures. They found that bisoprolol reduced the incidence of death from cardiac causes and nonfatal myocardial infarction within 30 days by 91% (!) (6).

However, after careful analysis of both studies significant methodological flaws have been discovered. The main limitation of Mangano´s trial is that patients already treated by beta-blockers and randomized into placebo group had them discontinued on entry to the study. Thus, they were at risk of beta-blocker withdrawal symptoms. In addition, in their analyses the researchers completely ignored 6 deaths occurring in hospital. In case of taking in these fatal cases into account, the statistically significant effect of beta-blockade on survival would disappear. Furthermore, it is not clear why short-term atenolol administration should have an impact on outcome within two years. In contrast to unselected population in Mangano´s trial Poldermans et al. studied a highly selected group of patients because they included only 112 (8%) from 1351 screened patients. Their study was besides not blinded, also the standard therapy in the placebo group was not clearly defined. The results of this study are thus valid only for such exactly defined population of patients (i.e. patients with stress inducible myocardial ischemia undergoing vascular surgery) and cannot be simply generalized for all patients undergoing other non-cardiac procedures.

Nevertheless, based mainly on these two studies authoritative Guidelines of the American College of Cardiology / American Heart Association on Perioperative Cardiovascular Evaluation for Noncardiac Surgery from 2002 (7) and updated in 2006 (8) stated that beta-blocker administration in the perioperative period is recommended in these cases:

1. Beta-blockers should be continued in patients undergoing surgery who are already receiving them to treat angina, symptomatic arrhythmias, hyper-

tension or other ACC/AHA class I guideline indications (recommendation of class I, i.e. treatment is beneficial, useful and effective; level of evidence C, i.e. recommendation is supported only by consensus opinion of experts, case studies or standard of care).

2. Beta-blockers should be given to patients at high cardiac risk owing to the finding of ischemia on preoperative testing who are undergoing vascular surgery (class I; level of evidence B, i.e. data derived from single randomized trial or from non-randomized studies).

Briefly, beta-blockers should never be discontinued in the perioperative period if patients are already treated and should be given to vascular surgical patients at high risk of cardiac complications. Regarding initiation of the treatment see below.

Except for these two explicit class I indications the ACC/AHA Guidelines further state:

3. Beta-blockers are probably recommended for patients with coronary artery disease or at high cardiac risk defined by the presence of multiple risk factors (i.e. advanced age, uncontrolled hypertension, left ventricular hypertrophy, low functional capacity, history of stroke, heart failure, diabetes, renal insufficiency, arrhythmias) undergoing vascular surgery or other procedures with intermediate (thoracic, abdominal or orthopedic) or high cardiac risk (emergent major procedures, operations on aorta or peripheral arteries or procedures associated with major blood loss) (class IIa, i.e. weight of evidence / opinion in favour of usefulness / efficacy; level of evidence B).

4. Beta-blockers may be considered in patients with intermediate cardiac risk defined by the presence of only one clinical risk factor on preoperative evaluation undergoing intermediate or low-risk surgical procedures including vascular surgery (class IIb, i.e. usefulness / efficacy is less well established by evidence / opinion; level of evidence C) or in patients with low cardiac risk undergoing vascular surgery, who are not currently on beta-blockers (level of evidence C).

5. Beta-blockers should not be given to patients undergoing surgery, who have absolute contraindications to beta-blockade (level of evidence C).

Additional randomized controlled trials evaluating perioperative beta-blocker administration were performed after 2000. Their design lacked flaws inherent to the studies by Mangano (5) et Poldermans (6). However, authors of these newer studies failed to confirm the beneficial effects of perioperative beta-blockers suggested in those older trials. In MAVS trial (Metoprolol After Vascular Surgery), which included 497 beta-blocker-naive patients undergoing vascular surgery, the investigators have not found any differen-

ce in combined endpoint of cardiac mortality and morbidity within 30 days (9). The authors of the DIPOM trial (Diabetic Postoperative Mortality and Morbidity) performed in 921 diabetic patients undergoing non-cardiac surgery lasting more than one hour, also failed to demonstrate any difference in combined endpoint of all-cause mortality, MI, unstable angina or congestive heart failure during a follow-up period of 18 months (range 6-30 months) between active (metoprolol 100 mg daily during the length of stay in the hospital) and placebo groups (10). Similarly, POBBLE (Perioperative Beta-Blockade) investigators compared metoprolol in a dose of 100 mg and placebo in 103 patients undergoing vascular procedures below renal arteries and have not shown any difference in combined endpoint of postoperative cardiac events within 30 days (11). Due to these negative findings results of currently ongoing trials POISE (PeriOperative Ischemic Evaluation, 10 000 patients in 11 countries) and DECREASE IV (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo) are eagerly expected in the end of 2007 or in spring 2008.

Inconsistent conclusions for perioperative beta-blockade were also found in meta-analyses of published trials – Auerbach (12, 13), Stevens (14), McGory (15) and Schouten (16) demonstrated beneficial effects, while Devereaux et al. (17), who included most studies (22) and patients (24,37), could not prove any significant effect of perioperative beta-blockade on overall as well as on cardiac mortality. On the contrary, Devereaux et al. emphasized an increased risk of bradycardia and hypotension requiring treatment. All of us can certainly remember patients with hypovolemia, sepsis or decreased myocardial contractility, in which acutely initiated beta-blockade distorted their fragile hemodynamic balance.

Negative effects of perioperative beta-blockade also appeared in the huge observational study done by Lindenauer et al. (18), who processed data from 663 635 patients in 329 hospitals throughout USA. They concluded that perioperative beta-blocker administration in patients with low cardiac risk (defined by Lee Revised Cardiac Risk Index 0 or 1) is unwarranted because these patients may be harmed. Increased risk of death in them can likewise probably be explained by hypotension and/or bradycardia with diminished cardiac output. These findings were further confirmed by Biccard et al. (19) who performed meta-analysis of the data from previously published prospective randomized controlled trials of acute perioperative beta-blockade on incidence of perioperative myocardial ischemia in patients with intermediate risk (defined by Lee Revised Cardiac Risk Index ≤2) or undergoing intermediate risk procedures in general surgery or orthopedics. Biccard et al. compared the incidence of postoperative cardiovascular complications

associated with perioperative myocardial ischemia. They showed that acute beta-blockade really decreased the incidence of perioperative ischemia but had only a small effect on the incidence of cardiovascular complications within 12 months after the surgery. They concluded that beta-blocker administration in patients with ≤ 3 clinical risk factors undergoing non-vascular surgical procedures is not warranted (19).

When indicating perioperative beta-blocker therapy it is also necessary to remember that cardioprotective effect of these drugs is obviously inherent to the whole group but that there are significant differences among individual drugs. Atenolol, bisoprolol, esmolol and most often metoprolol were studied in trials of perioperative beta-blocker administration. Metoprolol is a lipophilic, cardioselective drug acting on beta-1 adrenergic receptors with a relatively short-term effect (elimination half-time 3-7 hours). However, metoprolol is metabolized by the polymorphic cytochrome P450 (CYP) 2D6 isoenzyme and that causes widely variable drug levels in different individuals. In population there are poor (6-10%), intermediate, rapid and even ultrarapid metabolizers (5 %) who may not achieve an optimal target concentrations with recommended doses (20). On the other side, despite more than 10-fold different levels of metoprolol in plasma between poor and ultrarapid metabolizers metoprolol pharmacodynamics differed only by less than 2-fold and there was only a marginal difference in metoprolol efficacy on heart rate between these groups (21). In addition, the activity of particular CYP 2D6 isoenzyme can be further modified by different activators or inhibitors (e.g. amiodarone, propafenone). Similarly, carvedilol, a beta-1, beta-2 and alpha-1 adrenergic receptor blocking agent mostly used in heart failure, is also being metabolized by this isoenzyme. On the contrary, bisoprolol metabolism is not influenced by genetic heterogenity.

In clinical practice, the effect of beta-blocker administration on the heart can easily be assessed by measuring heart rate. In the preoperative period the heart rate should not exceed 60/min while in the postoperative period it can be higher but should not exceed the limit of ischemic threshold lowered by 20% (22,23). Ischemic threshold can be diagnosed most easily on Holter monitoring and is defined as the lowest heart rate at which ST-segment depression occurs (22). Tight heart rate control seems to be a key element for reduction of peri- and postoperative myocardial ischemia and adverse cardiac events (24). This is also confirmed by the well-known fact that maintaining heart rate in the predetermined range is easier before and during the surgery, but could be a problem afterwards due to e.g. pain, hypovolemia, respiratory disturbances, fever. The appropriate dose of a particular beta-blocker should thus be titrated carefully.

The mechanism of beneficial cardioprotective beta-blocker effect is not completely understood. In generally, it is apparently caused by prevention of cardiotoxic effect of catecholamines secreted due to stress from medulla of adrenal glands or spilled-over from sympathetic synapses on the heart. It is associated with heart rate slowing resulting in lengthening of diastolic time and thus coronary blood flow in the left ventricle. With simultaneous reduction of contractility the ratio between myocardial oxygen supply and demand can be corrected. In addition, antiarrhytmic, antiinflammatory, antiapoptotic or metabolic effects can be important as well (25).

The beneficial effect of perioperative beta-blockade is also significantly influenced by genetic variations of adrenergic receptors. It was examined in the recently published Swiss Beta-Blocker in Spinal Anesthesia Study (26). The authors found that perioperative (10 days) bisoprolol administration in elderly patients at-risk of cardiovascular complications undergoing surgical procedures in spinal anesthesia did not affect their cardiovascular outcome. However, the incidence cardiovascular complications was significantly higher in carriers of at least one allele with glycine at the position 389 in the genotype of the beta-1 adrenergic receptor than in carries of the more usual wild type receptor (32,4 % vs. 18,7%) containing both alleles with arginine at the same position (Arg389Arg), which was present in 60% of the study population. It seems that patients with defined adrenergic receptor genotypes may profit from beta-blockade, whereas others not. Adrenergic receptor genotyping could thus help to optimize perioperative beta-blocker therapy.

There is no doubt that beta-blocker withdrawal in the perioperative period may harm patients. On the other side, it seems that chronic beta-blocker therapy has not the same protective effect as acutely initiated blockade. It could be caused by an increase of number, density or sensitivity of beta-adrenergic receptors in chronic administration. Patients using beta-blockers chronically may thus require increased doses or use of alternative risk reduction strategies, such as calcium channel blockers or alfa-2 adrenergic receptor antagonists (27).

Other incompletely resolved issue is when and how to start and in some cases to discontinue perioperative beta-blocker administration. Beta-blockade seems not to be absolutely necessary in the preoperative period if the heart rate remains in the predetermined safe range. On the other side, it may be optimal to initiate beta-blocker administration in time and in stable patients, i.e. sufficiently before the surgery and to titrate the dose similarly as in heart failure patients. However, in our practice this approach is almost always impossible. With regard to the occurrence of perioperative myocar-

dial infarction the most important is to control heart rate tightly during the first postoperative days (48-72 hours). Maintaining an adequate blood pressure and cardiac output is also essential. Beta-blocker administration should then continue in patients with low or intermediate risk for at least a week, in high-risk patients one month and in patients with a clear class I ACC/AHA indication for beta-blocker administration it depends on this indication (25).

In summary, according to the current level of evidence the routine beta-blocker administration to almost all patients undergoing non-cardiac surgery as a measure of quality is not warranted in contrast to judicious beta-blocker use in the management of high-risk patients.

1. Beta-blockers are clearly indicated in patients with class I indication according to the ACC/AHA Guidelines, i.e. in patients already treated by them or in high-risk patients in vascular surgery. To initiate beta-blocker administration acutely is recommended in patients, who are not using them but have a class I ACC/AHA indication for them that is not associated with the current surgery (e.g. patients after myocardial infarction or with left ventricular dysfunction without contraindications). These patients should receive beta-blockers mainly for their long-term benefit. Beta-blockers should also be given to patients requiring heart rate and/or blood pressure control in the perioperative period (28).
2. Beta-blocker of choice is currently not known, longer-acting drugs seem to be more beneficial (29,30).
3. Tight heart rate control is obviously the key for dose determination (24).
4. There is no consensus regarding the time for initiation and/or discontinuation of beta-blocker administration in the perioperative period.

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