# Perioperative β-Blocker Therapy

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All β-adrenoceptor-antagonists (in the following referred to as "β-blockers"), except those with intrinsic sympathetic activity, reduce mortality in both myocardial infarction (1,2) and heart failure patients (3,4). Randomized clinical trails involving more than 24,000 patients have shown that β-adrenoceptor-antagonism (in the following referred to as "β-blockade") reduces post-myocardial infarction mortality, probably by a reduction in infarct size and in ventricular arrhythmias (5). On the basis of such information it seems logical that perioperative β-blocker therapy should be beneficial during the period of perioperative stress.

Activation of the hypothalamus-pituitary-adrenal axis persists for at least 1 wk after surgery. Adrenal cortical stimulation is accompanied by sympathetic nervous system-induced adrenal medullary activation resulting in the release of catecholamines with subsequent stimulation of adrenergic receptors. Adrenergic receptors are located in virtually every organ. In the human heart, they mediate numerous biological responses, including inotropy, chronotropy, myocyte apoptosis and direct myocyte toxicity. Thus, catecholamines increase each of the four determinants of myocardial oxygen consumption (i.e., heart rate, preload, afterload, and contractility).

Indications for the perioperative use of β-blockers have included hypertension (persistent or transient), induced hypotension, dissecting aortic aneurysm (in an attempt to decrease developed left ventricular pressure), hypertrophic (obstructive) cardiomyopathy (also in an attempt to decrease developed left ventricular pressure), pheochromocytoma, and thyrotoxicosis. Recently, documented or risk factors for coronary artery disease have been added to this list of indications (6). This is based on the potential of β-blockers to reduce myocardial oxygen consumption (thus improving the myocardial oxygen supply/demand balance) by decreasing sympathetic tone and myocardial contractility, in turn resulting in decreases of heart rate and blood pressure. Furthermore, they decrease $\beta_2$-adrenoceptor-mediated release of intracardiac norepinephrine during ischemia (reducing cardiac toxicity), they attenuate exercise-induced coronary vasoconstriction (improving exercise capacity), and they have antiarrhythmic properties (increasing the threshold for ventricular fibrillation during myocardial ischemia). This review lecture will address primarily the issue of whether perioperative β-blocker therapy may possibly improve perioperative cardiac outcome in patients at increased risk for adverse outcome.

## Results of Randomized Controlled Trials on Perioperative β-Blocker Therapy

### *Effect on Perioperative Myocardial Ischemia*

Several studies have examined the effect of perioperative β-blocker therapy on perioperative myocardial ischemia (7–10), and several have found a reduction in the incidence of myocardial ischemia in patients receiving β-blockers perioperatively (7–9). The results of these studies are very difficult to put into proper clinical perspective because of markedly different study populations, surgical procedures, β-blocker management, and targeted heart rate. The incidence of perioperative myocardial ischemia in untreated control patients varied between 15% (10), 28% (7), 39% (8), and 73% (9), reflecting an entirely different baseline risk for adverse perioperative cardiac outcome. In the presence of such differences in baseline cardiac risk, it is not at all surprising that the respective incidence of perioperative myocardial ischemia in those patients receiving β-blockers also varied tremendously between 6% (10), 2% (7), 24% (8), and 33% (9), reflecting clearly varying degrees of myocardial protection afforded by β-blockers. As a matter of fact, one of these studies (10) did not find any statistically significant effect of β-blockade on perioperative myocardial ischemia. However, this finding was almost to be expected. The mere 6% incidence of perioperative myocardial ischemia in those patients not receiving β-blockers indicates low risk for adverse perioperative cardiac outcome in these patients undergoing an intermediate-risk (total knee arthroplasty) rather than a high-risk surgical procedure (e.g., vascular surgery). It can thus not be expected that β-blockers provide additional protection. Nevertheless, irrespective of individual findings, myocardial ischemia is considered a

"soft" outcome, i.e., a surrogate measure of "hard" outcome parameters like cardiac death, nonfatal myocardial infarction, unstable angina, congestive heart failure, life-threatening cardiac arrhythmias, or the need for coronary revascularization.

### *Effect on Perioperative Cardiac Mortality*

Such "hard" outcomes have been assessed in two, much discussed studies (11,12). In a randomized, double-blinded, placebo-controlled study, Mangano et al. (11) looked at the potential benefit of perioperative atenolol in patients with or at risk for coronary artery disease undergoing major noncardiac surgery under general anesthesia. Atenolol (n = 99) or placebo (n = 101) were started IV approximately 30 min before induction of anesthesia and continued until hospital discharge or for up to 7 days postoperatively. Outcome parameters included cardiac death (death attributable to myocardial infarction, dysrhythmia, or congestive heart failure) and cardiac events (nonfatal myocardial infarction, unstable angina, and/or congestive heart failure requiring admission and treatment, myocardial revascularization) during the 2 yr after hospital discharge (i.e., in-hospital cardiac morbidity and mortality were not included in the analysis). Over the 2-yr follow-up period, overall mortality after hospital discharge was significantly lower in the atenolol group (10%) than in the placebo group (21%, P = 0.019). The main reason for this difference was a reduction in cardiac deaths during the first 6 mo in the atenolol-treated patients. The combined cardiovascular outcomes were similarly reduced in the atenolol group.

The study has been criticized on numerous grounds. 1) In-hospital cardiac morbidity and mortality were not included in the final analysis. Four patients in the atenolol group and two patients in the control group died during hospitalization. Although a statistically significant difference between treatment and placebo groups remains when these cases are included in the final analysis, the data become, nevertheless, less "impressive." 2) The potential for acute β-withdrawal symptoms in the control group cannot be excluded. Eight patients on chronic β-blocker medication were acutely taken off their β-blockers when they were randomized to the control group. Thus, acute β-withdrawal symptoms could possibly have contributed to the less favorable outcome in the placebo group. 3) Roughly 40% of patients did not tolerate the full dose, and roughly 15% did not tolerate atenolol at all. 4) Female gender was underrepresented. 5) The exact number of patients with intermediate rather than high risk for adverse perioperative cardiac outcome is not specified. 6) There is a trend towards a more severe cardiac history (i.e., previous myocardial infarction, angina, diabetes, coronary revascularizations, advanced age) in the placebo group, and a trend towards more effective cardiac therapy (i.e., β-blockers, angiotensin-converting enzyme inhibitors) at hospital discharge in the atenolol group. Despite such obvious limitations, the American College of Physicians stated that "... this trial is sufficiently convincing, in the absence of contradictory evidence, that it is now appropriate to give atenolol to patients who meet the above criteria as long as no serious contraindications (such as asthma) are present" (13).

A subsequent study by Poldermans et al. (12) looked at the potential benefit of perioperative bisoprolol in patients with documented coronary artery disease (diagnosed by new wall motion abnormalities on dobutamine stress echocardiography) undergoing major vascular surgery. In this study, 1351 patients scheduled for elective major vascular surgery were screened for cardiac risk factors (i.e., age >70 yr, angina, prior myocardial infarction, compensated or a history of congestive heart failure, current treatment for ventricular arrhythmias, current treatment for diabetes mellitus, or limited exercise capacity). Of the 1351 patients, 846 had at least one of these cardiac risk factors. These 846 patients were, in turn, screened for a positive dobutamine stress echocardiogram (DSE). Of the 846 patients, 173 had such a positive DSE. Of these 173 patients, 61 were excluded from further study because of either extensive wall motion abnormalities on DSE, strong evidence on DSE for left main or severe three-vessel coronary artery disease, or because they were already taking β-blockers. The remaining 112 patients were randomized to receive either bisoprolol (n = 59) or "standard care" (n = 53). Bisoprolol was started on average 37 (range 7–89) days before surgery and was continued for 30 days postoperatively. Outcome parameters included cardiac death and nonfatal myocardial infarction during the first 30 days after surgery. The authors reported a 10-fold lower rate of perioperative cardiac events in the bisoprolol group compared with the "standard care" group (3.4% vs 34%; P = 0.001).

Although the results would suggest that patients with documented coronary artery disease undergoing high-risk surgery benefit from perioperative β-blockade, this investigation also has several limitations (1). The most important limitation is certainly the lack of blinding of the treatment (2). "Standard care," as provided in the control group, is not defined (3). This is a highly selective study population. Of the 1351 patients that were initially screened, only 112 (8%) where eventually included in the actual study. Thus, the results are not necessarily representative for a broader patient population (4). In view of the small study size, the possibility that the statistically "highly significant" differences occurred by chance alone cannot entirely be ruled out (5). Finally, the 34% complication rate in the "standard care" group (nine cardiac deaths, nine myocardial infarctions) is rather high. A high complication rate in the control group generally tends to

"favor" the treatment group. Despite the various limitations, the accompanying editorial stated that "... In the absence of major contraindications therapeutic doses of β-adrenergic antagonists should be given to patients with an intermediate or high risk of cardiac complications" (14).

## *Unanswered Questions*

Based on the findings by Mangano et al. and Poldermans et al., the use of perioperative β-blockade has been advocated repeatedly (14–16). Nevertheless, several questions remain.

*Should β-blockers be administered together with other sympatholytic therapies?* The safety of simultaneously administering β-blockers in patients receiving thoracic epidural anesthesia or $\alpha_2$-adrenergic agonists has not been established. It is conceivable that the interaction between treatments causes an unacceptably high incidence of bradycardia and hypotension, counteracting any potential cardioprotective effect of β-blocker therapy. At present, it remains unknown whether it is at all necessary to add β-blockers to treatments like $\alpha_2$-adrenergic agonists that have demonstrated themselves some degree of cardioprotective potential in the perioperative period (17).

*Is there a β-blocker of choice for perioperative β-blocker therapy?* Blocking or blunting the perioperative adrenergic stress response is most likely the key pathophysiologic intervention that associates perioperative β-blocker therapy with improved cardiac outcome. Therefore, although not proven yet, it is rather unlikely that pharmacological differences between β-blockers (e.g., in receptor selectivity and affinity, lipophilicity, and intrinsic sympathomimetic activity) have any impact on efficacy and safety of treatment. Choice of the β-blocker should be based on the admittedly very few controlled randomized trials that have demonstrated effectiveness of perioperative β-blocker therapy. Any cardioselective β-blocker (such as atenolol, bisoprolol or metoprolol) is probably an acceptable choice. Atenolol and bisoprolol were the two drugs that had been administered in those two studies that are highly suggestive of a cardioprotective effect of perioperative β-blocker therapy (11,12).

*When should perioperative β-blockade be started?* In the two most relevant studies on this subject, perioperative cardioprotection was demonstrated when the medication had been initiated either weeks before the scheduled surgery (12) or as late as during induction of anesthesia (11). The recently revised ACC/AHA guidelines on perioperative cardiovascular evaluation for noncardiac surgery (6) recommend that in patients with Class I indications for perioperative β-blocker therapy, β-blockers be started days or weeks before elective surgery. This makes sense, as it will allow titration of the β-blocker to the targeted heart rate.

*What should be the therapeutic goal?* It is assumed that cardiovascular and sympathetic suppression is required to produce cardiac protection. The extent of such suppression is difficult to assess clinically. Basically all studies on the perioperative use of β-blockers have, therefore, taken heart rate as physiologic surrogate of sympathetic tone (11,12). Preoperatively, β-blockers were titrated to achieve heart rates between 50 and 60 bpm (12). Postoperatively, heart rates of <80 bpm (10–12) or 20% below the preoperative ischemic threshold (9) were targeted. The revised ACC/AHA Guidelines recommend that the preoperative dose be titrated to achieve a resting heart rate between 50 and 60 bpm (6). Surprisingly and somewhat unexpectedly, perioperative β-blockade does not reduce the neuroendocrine stress response, (18) suggesting that blunting of this stress response is not necessarily the primary mechanism responsible for any possible cardioprotective effect of perioperative β-blockade.

*For how long should β-blocker therapy be continued postoperatively?* In the two main controlled, randomized trials on the effectiveness of perioperative β-blocker therapy, β-blockers were continued for up to a week (11) and up to a month (12) after surgery. After the initial study period of 30 postoperative days, the 101 survivors in the Poldermans et al. study (12) continued to receive either bisoprolol therapy (n = 57) or standard care (n = 44) according to their initial randomization (19). In the bisoprolol group, the dose was adjusted to achieve a heart rate between 50 and 60 bpm. Patients were followed for 11–30 mo after surgery, with a median duration of 22 mo. Cardiac events (cardiac death and non-fatal myocardial infarction) occurred in 7 (12%) patients of the bisoprolol group and in 14 (32%) patients of the standard care group (P = 0.025). These results suggest that long-term postoperative β-blockade reduces the incidence of late cardiac events, certainly among survivors of major vascular surgery who had received perioperative β-blockade.

It appears intuitively obvious that those patients with objective indications for the use of β-blockers should continue β-blocker therapy after hospital discharge. In patients without clear indications for long-term β-blocker therapy, β-blockers should probably be continued for at least the time of hospitalization, preferably for up to 1 mo postoperatively. In those patients in whom β-blocker therapy is going to be discontinued after discharge, the dose should be tapered slowly to avoid acute withdrawal symptoms. In those patients in whom β-blocker therapy is going to be continued after discharge, the dose should be adjusted as indicated.

*Is there a risk of discontinuing perioperative β-blockade?* It is conceivable that acute withdrawal symptoms could develop when β-blockade is abruptly discontinued in patients at increased cardiac risk who were started preoperatively on β-blockers. Although

neither of the controlled randomized trials reported such adverse effects of discontinuation of β-blockers, (11,12) results of a retrospective analysis in a small number of patients would suggest that discontinuation of β-blockers in vascular surgery patients may be associated with an increased risk of postoperative morbidity and mortality (20). Four of 8 patients (50%) whose β-blocker therapy was discontinued died compared with only 2 of 132 patients (1.5%) who were continued on β-blockers. It thus seems advisable to discontinue β-blocker therapy gradually (and only after a period of preferably 30 days postoperatively) in those patients not considered to have a clear indication for long-term therapy.

*Is "routine" chronic β-blocker therapy continued perioperatively as effective as acute, closely monitored, heart rate-targeted perioperative β-blocker therapy?* In the Poldermans et al. study (12), 53 patients were excluded from the study because they were already taking β-blockers. These patients subsequently underwent planned vascular surgery under continued but not specified β-blocker therapy. In this subpopulation, the 30-day perioperative cardiac mortality was 7.5%, twice as high as that reported in the randomized part of the trial (3.4%). These findings would suggest that perioperative β-blocker therapy might be less effective when not closely monitored and strictly heart rate targeted. Somewhat surprisingly, although the respective findings are listed, the authors do not comment on these findings at all.

The total cohort of 1351 consecutive patients initially screened in the randomized trial on bisoprolol (12) was subsequently reanalyzed (21). Of the 1351 patients scheduled for major vascular surgery (thus, per definition, at high risk of perioperative adverse cardiac outcome), 360 (27%) received β-blockers perioperatively, whereas 991 (73%) did not. Again, β-blocker management in those 360 patients was not specified (except for those 59 patients who were part of the randomized trial). The perioperative cardiac event rate (nonfatal myocardial infarction, cardiac death) was 2.2% (n = 8) in the β-blocker-treated patients (comparable to the 3.4% event rate reported in the randomized part of the trial) and 3.7% (n = 37) in the non-β-blocked patients (almost 10-fold lower than the 34% event rate reported in the randomized part of the trial). The finding of a comparably low perioperative cardiac event rate in this larger population of β-blocked patients (who, presumably, were less intensively monitored than those patients who participated in the prospective, controlled trial) could be interpreted as suggestive evidence that "routine" chronic β-blocker therapy continued perioperatively is, in fact, as effective as acute, closely monitored, heart rate targeted perioperative β-blocker therapy.

*Is it possible to formulate indications and contraindications for the use of perioperative β-blocker therapy?* Should all patients with any kind of cardiac risk factor scheduled for any kind of surgical procedure receive perioperative β-blocker therapy? Or only patients with documented coronary artery disease undergoing surgery that is usually associated with a high incidence of perioperative cardiac complications (such as major vascular surgery)? As mentioned above, of the 1351 patients initially screened in the randomized trial on bisoprolol (21), 360 (27%) received β-blockers perioperatively, whereas 991 (73%) did not. The perioperative cardiac event rate was 2.2% (n = 8) in the β-blocker-treated patients (comparable to the 3.4% event rate reported in the randomized part of the trial), and 3.7% (n = 37) in the non-β-blocked patients (almost 10-fold lower than the 34% event rate reported in the randomized part of the trial). Why would there be a 10-fold difference in perioperative cardiac event rate between β-blocked and non-β-blocked patients in the randomized prospective trial, but not even a two-fold difference in the entire population from which patients were recruited for that randomized trial? The likely explanation is that those patients receiving β-blockers perioperatively had a statistically significantly worse cardiac risk profile (reflected by a higher incidence of hypertension, ventricular arrhythmias, current or prior angina, prior myocardial infarction, prior coronary revascularizations, and long-term cardiac medications) than those not receiving β-blockers. Thus, in contrast to the prospective trial, groups presenting for retrospective analysis were not comparable to start with. Despite such worse cardiac risk profile in the patients receiving β-blockers, the outcome was better in the treated than in the non-β-blocker-treated patients (although the difference is far less impressive than that observed in the prospective randomized trail). This part of the results could therefore be interpreted as suggesting that perioperative β-blocker therapy is of particular benefit in patients at higher cardiac risk. On the other hand, the relatively low incidence of perioperative cardiac events in those patients who were not β-blocked would suggest that not all patients undergoing high-risk vascular surgery require perioperative β-blockade.

Other parts of this retrospective analysis would tend to support such reasoning. Of the 1351 vascular surgery patients who were initially screened, 1118 (83%) had at most 1 or 2 clinical risk factors (defined as age ≥70 years, current angina, prior myocardial infarction, congestive heart failure, prior cerebrovascular event, diabetes mellitus, or renal failure). Among this subgroup of patients with relatively low cardiac risk, those receiving β-blockers perioperatively had a lower cardiac event rate (2/263 patients, 0.8%) than those not receiving β-blockers (20/855 patients, 2.3%). Among a further subset of 375 patients with no clinical risk factor at all, those receiving β-blockers tended to have a lower cardiac

event rate (0/48 patients, 0%) than those not receiving β-blockers (4/327 patients, 1.2%). However, these outcomes are not significantly different. Considering that these patients underwent major vascular surgery, the complication rate was very low, irrespective of perioperative β-blocker therapy.

By contrast, in the subgroup of 233 (17%) patients with ≥3 clinical risk factors, those receiving β-blockers had a cardiac event rate of 6.2% (6/97 patients) compared with a cardiac event rate of 12.5% (17/136 patients) in those not receiving β-blockers. Within this subgroup of patients with ≥3 clinical risk factors, 207 patients had 4 or fewer new wall motion abnormalities on dobutamine stress echocardiography. Those receiving β-blockers perioperatively had a lower cardiac event rate (2/86 patients, 2.3%) than those not receiving β-blockers (12/121 patients, 10.6%). However, in a further subgroup of 26 patients with ≥3 clinical risk factors and five or more new wall motion abnormalities on dobutamine stress echocardiography, there was no difference in the cardiac event rates between those receiving β-blockers perioperatively (4/11 patients, 36%) and those not receiving β-blockers (5/15 patients, 33%).

Before drawing conclusions from the findings of this retrospective analysis, we have to remember that this is a retrospective analysis, treatments were neither controlled nor randomized or blinded, and the small numbers of patients in some of the subgroups are too small to allow valid statistical analysis. Taking these limitations into consideration, these results would suggest that in patients undergoing vascular surgery perioperative β-blocker therapy may possibly be beneficial in all but subsets of very low or very high risk patients. The findings would further suggest indirectly that aggressive β-blockade in high-risk patients scheduled for high-risk surgery may reduce the need for additional preoperative noninvasive cardiac testing and coronary angiography. It is likely that the combined morbidity and mortality from the three sequential procedures coronary angiography, coronary revascularization, and subsequent major vascular surgery is higher than the 3.4% incidence of major cardiac complications in patients receiving perioperative bisoprolol (12). Only in a subset of patients with extensive myocardial ischemia, perioperative β-blocker therapy may not be sufficiently protective (21).

Based on the results of various recent studies, the revised ACC/AHA Guidelines (6) list several conditions as Class I indications for perioperative β-blocker therapy (i.e., conditions for which there is evidence for and/or general agreement that the therapy is useful and effective): 1) the need for β-blockers in the recent past to control symptoms of angina; 2) patients with symptomatic arrhythmias or hypertension; and 3) patients at high risk for a perioperative cardiac event based on the finding of myocardial ischemia on perioperative testing who are undergoing vascular surgery. Class IIa indications for perioperative β-blocker therapy (i.e., conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of the performed therapy, with the weight of evidence/opinion in favor of usefulness/efficacy of the performed therapy) include preoperative identification of untreated hypertension, known coronary artery disease, or major risk factors for coronary artery disease.

When it comes to defining the contraindications for the use of β-blockers, it is helpful to remember that the 2001 American Heart Association/American College of Cardiology Guidelines for secondary prevention of myocardial infarction and death recommend to initiate β-blockade in all post-myocardial infarction patients and to continue such therapy indefinitely (1). They list as absolute contraindications for the use of β-blockers symptomatic bradycardia (usually a heart rate <50–60 bpm), symptomatic hypotension (usually a systolic blood pressure <90–100 mm Hg), severe heart failure requiring IV diuretics or inotropes, cardiogenic shock, asthma or reactive airway disease requiring bronchodilator and/or steroids, and 2° or 3° atrioventricular block. For patients with less severe heart failure, COPD, diabetes mellitus, peripheral vascular disease and 1° atrioventricular block, guidelines for the initiation of β-blocker therapy have been provided (2).

## *Proposed Algorithm for the Use of Perioperative β-Blocker Therapy*

Taking into consideration the results of the various studies on perioperative β-blocker therapy, an algorithm for the use of perioperative β-blocker therapy based on preoperative risk stratification has recently been suggested (22). In patients with more than three major clinical risk factors (such as high-risk surgical procedures, ischemic heart disease, cerebrovascular disease, insulin-dependent diabetes mellitus, chronic renal insufficiency) (21) combined with a positive result in noninvasive additional cardiac tests, perioperative cardiac event rate will remain in the 6.5–16% range even with perioperative β-blocker therapy. In this patient population, additional therapies/interventions to reduce risk (e.g., coronary revascularization) should be considered.

In clinically high-risk patients with negative noninvasive test results, and in clinically intermediate risk patients (1–2 major clinical risk factors or any of two minor risk factors such as age ≥65 yr, hypertension, current smoker, serum cholesterol at least 240 mg/dL, non-insulin-requiring diabetes mellitus) (11) with good functional capacity and without evidence of angina or peripheral vascular disease, β-blocker therapy

is started preoperatively and surgery is performed as planned.

In clinically intermediate-risk patients with poor functional capacity and with evidence of angina or peripheral vascular disease, additional therapies/interventions to reduce risk (e.g., coronary revascularization) should be considered. Finally, in low-risk patients without clinical risk factors, perioperative cardiac event rate is low with (0.4%) or without (0.4–1.0%) perioperative β-blockade; therefore, perioperative β-blockade is deemed unnecessary.

## Conclusion

The newsletter of the Anesthesia Patient Safety Foundation reported in the summer issue of 2002 (23) that the Agency for Healthcare Research and Quality (AHRQ) had identified perioperative β-blocker therapy as one of 11 specific practices with sufficient clinical-based evidence for patient safety to justify immediate and widespread implementation (24). However, before a final recommendation for a liberal use of perioperative β-blockade can be made safely, several caveats have to be kept in mind. All studies that support use of perioperative β-blocker therapy have included rather small numbers of patients (as few as 26) (10). Often, recruitment of patients was highly selective and consecutive (recruitment rate as low as 8%) (12), excluding application of the results to an unselected surgical population. We have to further keep in mind that the beneficial effects were probably not only attributable to a rather aggressive therapy (targeted heart rates maximally 80 bpm) but also (and perhaps even more importantly) to continuous close monitoring of the patient. This will ensure both, optimal cardioprotection and patient safety. A more uncontrolled but equally aggressive postoperative administration of β-blockers on ordinary surgical floors might well result in more adverse side effects, possibly negating any beneficial effects. The title of a recent editorial is, therefore, a fair conclusion and recommendation: "Peri-operative β-blockade: a useful treatment that should be greeted with cautious enthusiasm" (25).

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