Anesthesiology 2009; 111:940–5

Perioperative Strokes and β-Blockade

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RECENTLY, the results of the PeriOperative Ischemic Evaluation (POISE) study have caused concern regarding β-blocker use in the perioperative setting.[1] Though β-blocker therapy was associated with an improved cardiac outcome, overall mortality was increased in the metoprolol-treated group. This was partially related to the increased incidence of postoperative stroke occurring early after surgery. These findings might have important implications on perioperative β-blocker use, not only for initiation of therapy before surgery in β-blocker naïve patients but also whether or not to continue therapy throughout surgery. This commentary reviews the incidence and pathophysiology of perioperative stroke and the relation of β-blockers and perioperative stroke, focusing on noncardiac surgery.

The risk of clinically apparent perioperative brain injury such as stroke varies widely among different types of surgery. Whereas patients undergoing general surgery appear to be at low risk (0.08–0.7%), those undergoing heart valve surgery and aortic arch repair have a high incidence of perioperative stroke (8–10%).[2] In Europe, 40 million general surgical procedures are performed annually. Therefore, it is estimated that 32,000–280,000 patients suffer from postoperative stroke. However, the true incidence of cerebral complications is probably underestimated because subtle forms of brain injury are commonly classified as delirium that may only be detected by rigorous neuropsychological testing.

The knowledge of the pathophysiology of postoperative cerebral complications is predominantly based on cardiothoracic surgery patients. It is estimated that 62% of strokes in this population have an embolic origin, 10% are related to hypoperfusion, and 10% have multiple causes.[2] Importantly, only 1% of strokes are caused by intracerebral hemorrhage. However, it should be acknowledged that the true pathophysiological basis of perioperative stroke is not as straightforward as it might seem. Embolic and hypoperfusion cerebral infarction most likely do not occur in isolation.[3] Impaired clearance of emboli (washout) seems to be the link between hypoperfusion, embolism, and ischemic stroke.[4] Intraoperative microemboli and low middle cerebral artery blood flow velocity are additive in predicting development of cerebral ischemic events after carotid endarterectomy.[5] Second, newer data wherein sensitive diffusion weighted magnetic resonance imaging (MRI) was performed suggest that as many as two-thirds of postcardiac surgery strokes have watershed or hypoperfusion pattern.[6] Finally, what appears to be occurring in cardiac surgery patients is that there is a rising prevalence of mostly unrecognized cerebral vascular disease concurrent with the rising age of our population. In fact, one study (that interestingly excluded patients with known cerebral vascular disease) found that as many as 75% of patients had evidence of impaired cerebral perfusion based on single photon emission computed tomography (SPECT) imaging before coronary artery bypass grafting (CABG) surgery.[7]

Approximately 45% of perioperative strokes are identified within the first day after surgery. The remaining 55% occur after uneventful recovery from anesthesia, from the second postoperative day onward. Early embolism results especially from manipulations of the heart and aorta or release of particulate matter from the cardiopulmonary-bypass pump. Delayed embolism is often attributed to postoperative atrial fibrillation, myocardial infarction resulting from an imbalance between myocardial oxygen supply and demand, and coagulopathy.

Compared to stroke after cardiac surgery, the pathophysiology of stroke after noncardiac surgery is ill defined. Perioperative hemodynamic instability and cardiac events, such as myocardial infarction and arrhythmias, likely play a major role. Recently, the POISE study identified a new risk factor for perioperative ischemic strokes: high-dose metoprolol succinate initiated for cardiac protection in patients undergoing noncardiac surgery.

Perioperative β-Blockade

β-Blockers in the nonsurgical setting are used widely and have proven effective in patients with documented

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Received from the Department of Anesthesiology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands. Submitted for publication November 13, 2008. Accepted for publication July 24, 2009. Supported by an unrestricted research grant from The Netherlands Organization of Health Research and Development (ZonMW), the Hague, The Netherlands (to Dr. O. Schouten), and by an unrestricted research grant from "Lijf & Leven" Foundation, Rotterdam, The Netherlands (to Dr. Hoeks). Dr. Fleisher was chair for the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. Dr. Poldermans has received educational grants from Merck (Merck KGaA, Darmstadt, Germany), Novartis (Novartis Pharma BV, Arnhem, The Netherlands), and Pfizer (Pfizer BV, Capelle a/d Ijssel, The Netherlands). These companies sponsored symposia during the European Society of Cardiology (ESC) Annual Sessions, which were chaired by Dr. Poldermans. Dr. Polderman is chair of the ESC Guidelines committee for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery.

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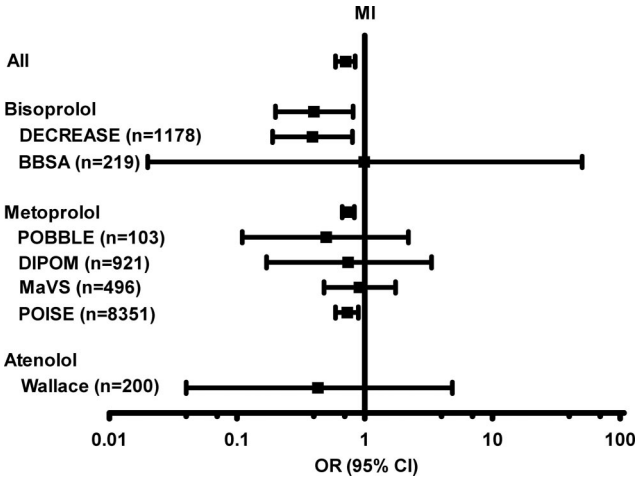

Fig. 1. Odds ratios (OR) of randomized β-blocker trials for perioperative myocardial infarction (MI). BBSA = beta blocker in spinal anaesthesia; CI = confidence interval; DECREASE = Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = metoprolol after surgery; POBBLE = perioperative beta-blockade; POISE = PeriOperative ISchaemic Evaluation trial.

coronary artery disease (CAD) to restore the balance of myocardial oxygen demand and supply.[8] Although initially contraindicated in patients with heart failure and peripheral atherosclerotic disease, β-blockers are now recommended therapy for these patients.[9,10] Similar to the nonsurgical setting, β-blockers are advocated for patients with documented CAD undergoing vascular surgery.[11] However, there is still controversy regarding perioperative β-blocker use in the general surgical population.

Several randomized studies have shown a beneficial cardiac effect of perioperative β-blocker use. In a placebo-controlled trial involving 200 high-risk patients, Mangano *et al.* found that atenolol (50 or 100 mg), administered intravenously beginning 30 min before surgery and then orally throughout hospitalization was discharged from the hospital (up to a maximum of 7 days), did not lower the risk of death from cardiac causes or myocardial infarction during hospitalization.[12] However, it did result in a 50% reduction in myocardial ischemia as assessed by continuous 48-h Holter monitoring. The authors observed a nonsignificant increase in incidence of stroke (*i.e.*, 4% *vs.* 1%, $P = 0.21$). The DECREASE study (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography) confirmed the benefits of β-blockers in noncardiac surgery. In a high-risk population of 112 patients with positive dobutamine echocardiography for CAD undergoing vascular surgery, the rate of perioperative cardiac death and myocardial infarction among patients who were randomly assigned to bisoprolol therapy (5 or 10 mg) started at least 30 days before surgery was 90% lower than that among patients assigned to standard care (3.4% *vs.* 34%).[13]

More recent studies have shown mixed results of β-blocker therapy (fig. 1).[14–17] The MaVS (Metoprolol after Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2 h before surgery until hospital discharge or a maximum of 5 days after surgery.[16] No significant differences in outcome were observed at 30 days after 6 months after surgery. The incidence of stroke in MaVs was 1.6% in controls and 2.0% in β-blocker users. In the POBBLE (Perioperative β-Blockade) trial, 103 patients undergoing vascular surgery were randomized to metoprolol or placebo, starting less than 24 h before surgery until 7 days after, and showed no difference in 30-day cardiovascular outcome.[14] Within 30 days, cardiovascular events occurred in 32% and 34% patients in the metoprolol and placebo groups, respectively (adjusted relative risk [RR] 0.87, 95% confidence interval [CI] 0.48–1.55), whereas stroke occurred in 2 of 53 *versus* 0 of 46, respectively. The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, which started therapy at the earliest in the evening before major noncardiac surgery, again showed no difference in 30-day cardiac outcome and a nonsignificant increase in strokes (0.4% *vs.* 0%).[15]

The mixed results of early β-blocker trials necessitated a large randomized trial. In the landmark study of the POISE investigators, 8,351 patients were randomly assigned to either metoprolol succinate controlled release or placebo. The primary endpoint of cardiac death, nonfatal myocardial infarction, or nonfatal cardiac arrest was reduced in the metoprolol controlled release (CR) group compared with placebo (5.8% *vs.* 6.9%, hazard ratio 0.84, 95% CI 0.70–0.99, $P = 0.04$). However, this beneficial cardiac effect was at the cost of an increased incidence of all-cause mortality and stroke. The incidence of stroke was increased from 0.5% to 1.0% ($P = 0.005$) in patients randomized to metoprolol treatment. Stroke was associated with perioperative hypotension, bleeding, atrial fibrillation, and a history of stroke or transient ischemic attack.

The recently concluded DECREASE IV trial, including 1,066 patients randomized in a 2 × 2 factorial design to receive perioperative β-blocker, *i.e.*, 2.5 mg of bisoprolol started a median 34 days before surgery and/or statins *versus* no additional medical therapy, showed that β-blocker use was associated with 67% RR reduction in the endpoint of nonfatal myocardial infarction and cardiac death ($P = 0.002$).[18] Patients on β-blocker therapy had a stroke incidence of 0.8% *versus* 0.6% in patients not on β-blockade.

Perioperative β-Blocker Therapy and Stroke

The increased risk for perioperative stroke in the POISE trial has caused serious concerns on the safety profile of perioperative β-blocker therapy. In patients with a diseased cerebrovascular tree, perioperative hypotension, and bleeding, an increased incidence of

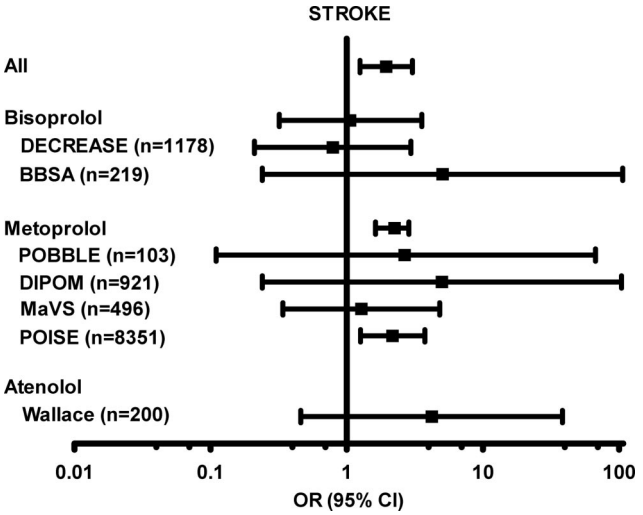

Fig. 2. Odds ratios (OR) of randomized β-blocker trials for perioperative stroke. BBSA = beta blocker in spinal anaesthesia; CI = confidence interval; DECREASE = Dutch Echographic Cardiac Risk Evaluating Applying Stress Echo; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = metoprolol after surgery; POBBLE = perioperative beta-blockade; POISE = PeriOperative ISchaemic Evaluation trial.

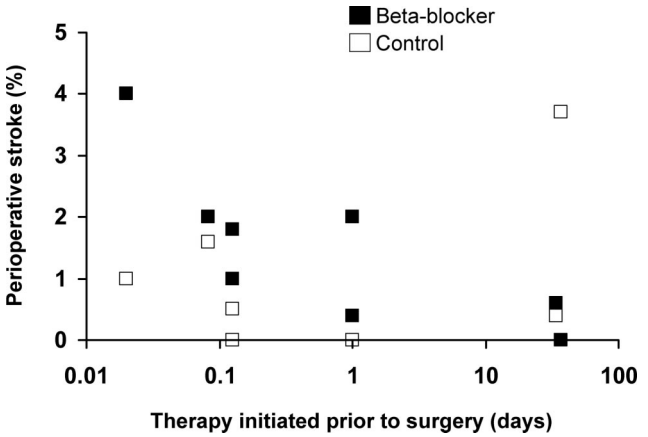

Fig. 3. Relation between timing of initiation of β-blocker therapy and the risk for perioperative stroke.

ischemic strokes was observed in those randomized to metoprolol. This has been augmented by the meta-analysis published in the same Lancet article.[1] The meta-analysis demonstrated that overall perioperative β-blocker therapy was associated with a 2.19-fold (95% CI 1.06–4.50) increased risk for nonfatal perioperative stroke; however, the DECREASE I and IV studies were not included.

Recently, Bangalore *et al.* published a meta-analysis on the effect of perioperative β-blocker therapy, including 12,306 patients.[19] The results of this meta-analysis seem to confirm the findings of the POISE trial: a decrease (OR 0.65, 95% CI 0.54–0.79) in nonfatal myocardial infarction (number needed to treat 63) at the expense of an increase (OR 2.01, 1.27–3.68) in nonfatal strokes (number needed to harm 293). The authors concluded that current evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having noncardiac surgery. Importantly, the impact of different dosing regimens, timing of initiation and type of β-blocker therapy were not fully appreciated in these analyses. If the results of DECREASE I and IV are added to the meta-analysis, β-blockers are still associated with an increased risk for perioperative stroke. However, as is shown in figure 2, the overall result in the randomized low-dose bisoprolol studies show no association with perioperative stroke at all (OR 1.06, 95% CI 0.32–3.56) in contrast to studies using metoprolol (OR 2.07, 95% CI 1.27–3.39). It should be noted that the cardioprotective effect was clear for both β-blocker types; OR for bisoprolol 0.40 (95% CI 0.20–0.81) and OR for metoprolol 0.74 (95% CI 0.61–0.89, figure 1). The key question is whether it is the type of β-blockers that makes the difference and whether other factors play a significant role in these results. Considering this, there are several potential pitfalls in the perioperative administration of β-blockers that should be considered, including timing of initiation of therapy, dosage of β-blockers, the impact of β-blocker withdrawal, and treatment targets.

Timing

Timing of initiation of perioperative β-blocker therapy seems to play a pivotal role in the risk of stroke, as shown in figure 3. In patients undergoing surgery in which β-blocker therapy is initiated within hours before surgery, there might be an increased risk of hypotension and bradycardia if β-blockers are administered too aggressively. The response to β-blocker therapy cannot be adequately monitored during this short period of time leading to a danger of overdosing. Although the sympathico-inhibitory effects of β-blockers occur almost instantly, the antiinflammatory effects may be observed only after prolonged treatment. As mentioned, in the Mangano *et al.* study, the major benefits of atenolol were observed in the months after surgery.[12] In studies starting β-blocker therapy hours before surgery, the incidence of postoperative stroke was higher compared to those who were on β-blockers for at least a week before surgery. It should be noted that the same study group performed the two trials that started β-blockade weeks in advance of surgery, using bisoprolol. Although bisoprolol is not commonly used in the United States for patients with proven CAD, it would be interesting to determine whether other centers achieve similar results with this low-dose bisoprolol regimen. In most nonsurgical studies, in particular in heart failure, there is a similar up-titration of β-blockers. In other words, β-blocker therapy is started at a relative low dose and is subsequently up-titrated according to blood pressure and heart rate. This approach has been shown to be effective and safe in heart

failure patients.[9] Importantly, patients on chronic β-blocker therapy should continue their therapy in the perioperative period because sudden β-blocker withdrawal increases the risk of adverse cardiac events.[20]

Dosing

Closely related to the issue of timing in perioperative β-blocker therapy is the question regarding what dosing scheme should be used. In contrast to other β-blocker studies, patients randomized in the POISE trial could receive up to 400 mg of metoprolol succinate controlled release the day of surgery; 100 mg 2–4 h before surgery, another 100 mg within 6 h after surgery, and 200 mg within 12–18 h after the first postoperative dose. The use of high-dose β-blocker therapy may block the heart rate response to cope with hypotension, *e.g.*, because of bleeding. In the nonsurgical setting, lower starting doses and slower up-titration are commonly recommended. For instance, in patients with heart failure, 12.5–25 mg/d is started for 2 weeks; for hypertension, the initial dose is 25–100 mg, usually increased at weekly intervals. This is important because a large proportion of high-risk elderly patients undergoing surgery may have some form of (asymptomatic) left ventricular dysfunction. The DECREASE IV treatment regimes start 2.5 mg of bisoprolol, which is approximately the same strength as 50 mg of metoprolol. The starting dose of metoprolol succinate in the POISE trial was 2–8 times the commonly prescribed dose for perioperative β-blocker therapy; other trials using metoprolol start usually at ranges from 50 to 100 mg/d.[14–16] It is noteworthy that in the DECREASE II trial starting with 2.5 mg of bisoprolol once daily, the target heart rate of 60–65 beats/min was achieved in approximately 75% of patients without dose adjustment.[21] For safety reasons, β-blocker therapy is withheld in case of a systolic blood pressure lower than 100 mmHg or a resting heart rate less than 50 beats/min. These criteria are nearly the same as used in the POISE study (100 mmHg or a heart rate below 45 beats/min).

Chronic β-Blocker Use and Stroke

Considering the results found in the POISE study, one should question what the effect of chronic β-blocker use on (postoperative) stroke is. In recent literature, questions are raised about whether β-blocker therapy should still be used as a first-line therapy for hypertension.[22–24] The use of β-blocker therapy as first-line treatment for hypertension was systematically evaluated in a Cochrane review by Wiysonge *et al.*[25] In this review, the effectiveness and safety of β-blockers on morbidity and mortality endpoints in adults with hypertension were evaluated. Compared to placebo, β-blocker therapy was associated with a significant decrease in stroke (RR 0.80, 95% CI 0.66–0.96). However, there was an increased risk for stroke compared to other blood-lowering medications; calcium-channel blockers (RR 1.24, 95% CI 1.11–1.40) and renin-angiotensin system inhibitors (RR 1.30, 95% CI 1.11–1.53). Considering these results, β-blockers should not be the drug of choice for the first-line treatment of hypertension.

These results, however, cannot be extrapolated to β-blocker use in the perioperative period. The initiation of β-blocker therapy in patients at risk for cardiovascular complications in the perioperative period focuses on lowering on heart rate rather than blood pressure. It would be interesting to see if patients undergoing noncardiac surgery, who are on chronic β-blocker use, would also be at risk for postoperative stroke.

In a study by van Lier *et al.* 186,779 patients who underwent noncardiac surgery were evaluated for postoperative stroke.[26] Patients with intracerebral surgery, carotid surgery, or head and/or carotid trauma were excluded. In total 34 patients (0.02%) experienced a stroke within 30 days after surgery. Chronic β-blocker use was as common in cases as in controls (29% *vs.* 29%; $P = 1.0$). The adjusted odds ratio for perioperative stroke among β-blocker users compared to nonusers was 0.4 (95% CI 0.1–1.5). Similar results were obtained in subgroups of patients according to the use of cardiovascular therapy and the presence of cardiac risk factors. These results show no increased risk for postoperative stroke after noncardiac surgery in patients on chronic β-blocker use. This favors the dosing regime used in the DECREASE studies, where β-blocker therapy is initiated well in advance and is carefully up-titrated to a desired effect.

Other Effects Related to β-Blocker Use and Stroke

Lemaitre *et al.*[27] investigated the interaction of variations in β-adrenegeric receptor genes with β-blocker use on the risk of MI and ischemic stroke. Several genetic variations in the β1-adrenergic receptor gene interacted with β-blocker use in both risks for MI and ischemic stroke. β-blocker use was associated with higher risk of combined MI, and ischemic stroke in carriers of rs#2429511 (OR 1.24, 95% CI 1.03–1.50) compared to carriers of common allele (OR 0.70, 95% CI 0.51–0.94). Two other major single nucleotide polymorphisms in β–adrenergic receptors genes (Ser49Gly and Arg389Gly) have been identified in several studies that might affect drug responses.[28–30] The role of these polymorphisms in the perioperative setting is still unclear.

A number of clinical studies have associated acute anemia with cerebral injury in perioperative patients. Two recent large observational studies have demonstrated that the incidence of adverse composite cardio-

vascular outcomes, including stroke, increases in anemic cardiac surgical patients when the preoperative hemoglobin level decreases below 12 g/dl.[31,32] In a study by Weiskopf *et al.*,[33] healthy human volunteers demonstrated impairment in central neuronal processing and cognitive function after acute isovolemic anemia. Concurrent exposure to additional risk factors such as surgical stress, drugs which limit cardiovascular compensatory responses (*e.g.*, β-blockers), hemodynamic instability, cardiovascular comorbidities, and advanced age could increase the risk of brain injury in perioperative patients. The combination of patients at risk of adverse cardiovascular complications, where the initiation of preoperative β-blocker therapy might be indicated, and acute perioperative isovolemic hemodilution deserves thorough investigation.

Finally, β-blockers have been implicated in altering glucose homeostasis, primarily through inhibition of pancreatic insulin secretion and promoting insulin resistance.[34–36] Insulin resistance is one of the main underlying physiologic processes that may lead to the metabolic syndrome. In a meta-analysis by Galassi *et al.*, it was indicated that individuals with the metabolic syndrome have a 61% increased risk of cardiovascular disease compared to individuals without the metabolic syndrome.[37] β-receptor selectivity appears to play a role in the degree of downstream metabolic effects, which include not only glucose increases but also weight gain and dyslipidemia. Nonselective and higher-dose selective agents result in the largest adverse metabolic changes. The mechanisms by which β-blocker treatment modifies insulin sensitivity are not yet fully understood, but several possibilities exist. Insulin clearance is reduced in hypertensive patients and β-blocker treatment appears to attenuate it further. As plasma insulin increases, the resulting hyperinsulinemia could downregulate the insulin receptors and consequently lower insulin sensitivity.

In conclusion, initiating prophylactic high-dose β-blocker therapy in patients undergoing noncardiac surgery is associated with fewer cardiac events but with an increase in strokes and mortality. However, if prophylactic β-blocker therapy is initiated at a low dose and up-titrated in the preoperative period, the risk of stroke seems to be similar to that of patients not on β-blockers while the cardioprotective effect is maintained. In these patients, strict hemodynamic control during surgery is mandatory. Preferably these results should be confirmed in a large-scale trial, starting β-blocker weeks before surgery at a low dose, as well as determining the optimal approach in patients at high-risk of perioperative cardiac morbidity and present the morning of surgery without having been placed on a β-blocker.

Patients on chronic β-blocker therapy should continue medication. In patients with proven coronary artery disease β-blocker therapy should be started sufficiently long before surgery to evaluate the hemodynamic impact. Importantly, hypotension and bradycardia should be avoided. Therefore a low-dose highly β1-selective drug is recommended.

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