Impact of Perioperative Bleeding on the Protective Effect of β-Blockers during Infrarenal Aortic Reconstruction

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ABSTRACT

Background: The use of β-blockers during the perioperative period remains controversial. Although some studies have demonstrated their protective effects regarding postoperative cardiac complications, others have demonstrated increased mortality when β-blockers were introduced before surgery.

Methods: In this observational study involving 1,801 patients undergoing aortic reconstruction, we prospectively assessed β-blocker therapy compared with no β-blocker therapy, with regard to cardiac and noncardiac postoperative outcomes using a propensity score approach. The impact of β-blockers was analyzed according to the intraoperative bleeding estimated by transfusion requirements.

Results: In-hospital mortality was 2.5% (n = 45), β-blocker use was associated with a reduced frequency of postoperative myocardial infarction (OR = 0.46, 95% CI [0.26; 0.80]) and myocardial necrosis (OR = 0.62, 95% CI [0.43; 0.88]) in all patients, but also with an increased frequency of multiple organ dysfunction syndromes (OR = 2.78, 95% CI [1.71;

What We Already Know about This Topic

- Whether chronic or acute administration of β-blockers improves or worsens perioperative outcomes remains controversial
- Some studies have suggested worsened outcomes in the face of major blood loss in patients taking β-blockers

What This Article Tells Us That Is New

- In this observational study, patients undergoing infrarenal aortic reconstructive surgery and who were receiving chronic β-blockade had fewer perioperative major cardiac adverse events
- In those with severe bleeding, death and multiorgan failure were more common in β-blocked patients

4.61]). In patients with severe bleeding (n = 163; 9.1%), the frequency of in-hospital death (OR = 6.65, 95% CI [1.09; 129]) and/or multiple organ dysfunction syndromes (OR = 4.18, 95% CI [1.81; 10.38]) were markedly increased. Furthermore, no more than 28% of the patients who died presented with postoperative myocardial infarction, whereas 69% of the patient with a postoperative myocardial infarction also presented an excessive bleeding.

Conclusions: Perioperative β-blocker therapy was associated with an overall reduction in postoperative cardiac events. In the vast majority of patients with low perioperative bleeding, the global effect of β-blockers was protective; in contrast, patients given β-blockers who experienced severe bleeding had higher mortality and an increased frequency of multiorgan dysfunction syndrome.

T HE use of β-blockers during the perioperative period remains controversial and lacks consensus as suggested by differences between European[1] and North American[2,3] guidelines. A number of studies have demonstrated clear benefits of β-blockers on postoperative cardiac adverse events,[4–8] whereas other studies have demonstrated no significant effect[9,10] or a deleterious effect on global mortality.[11] Several reasons could explain this inconsistency, including

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genetic variability in the response to β-blockers[12] or differences between the molecules or the doses used.[13]

Anemia induces a reduction in the transport of oxygen, which is compensated with an increase in cardiac output.[14] β-blockers limit this increase in cardiac output during maximal or submaximal exercise,[15] and if the heart remains protected. Conversely, hand organ perfusion may be reduced and other organ complications might appear without cardiac complication. Recently Beattie *et al.*[16] suggested that β-blockers may reduce the risk of myocardial infarction but may also increase the risk of perioperative stroke and mortality, especially when major blood loss occurs.

Our objectives were to examine whether perioperative hemorrhagic complications observed during major vascular surgery alter the effect of β-blockers. We also describe the relationship between postoperative cardiac complications and other postoperative complications (including multiple organ dysfunction syndrome, pneumonia, and death) after major vascular surgery.

Materials and Methods

Patient Characteristics

The Pitié-Salpêtrière Vascular Surgical Register is a recorded database, containing 194 clinical and surgical characteristics of all patients undergoing vascular surgery at our institution since 1984.[17,18] We included all patients who underwent infra-renal aortic reconstructive surgery (aneurysm or occlusive disease of the aorta), between January 2001 and December 2010. We excluded patients undergoing emergency. For each patient, the revised cardiac risk index (RCRI) was calculated (sum of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative treatment with insulin, and preoperative serum creatinine).[19] The study was approved by our institutional ethics committee (Comité Consultatif de Protection des Personnes Pitié-Salpêtrière, Paris, France).

Perioperative Management

All patients were screened in accordance with the recommendations of the American College of Cardiology/ American Heart Association Task Force.[20,21] A coronary angiography was performed in patients with poor or nonvaluable functional capacity, unstable coronary artery disease, or a positive noninvasive myocardial stress test. A percutaneous coronary procedure was performed at the time of catheterization when technically feasible, otherwise a coronary artery bypass graft was considered. Patients undergoing percutaneous coronary procedures received one or more bare-metal stents and were treated with clopidogrel for 4–6 weeks and aspirin. Aortic surgery was performed after a 4- to 6-week delay and after discontinuing aspirin for 1 week. Surgery was performed under general anesthesia with intravenous propofol, sufentanil, and atracurium, as described previously.[17,18]

Blood was obtained for measurement of cardiac troponin I from all patients on arrival at the postanesthesia care unit, and on postoperative days 1, 2, and 3. This measurement was performed using an immunoenzymofluorometric assay on a Stratus autoanalyzer (Dade-Behring, Paris La Défense, France). An electrocardiogram was performed on arrival at the postanesthesia care unit, and on postoperative days 1, 2, and 3, and after day 3 in the presence of clinical abnormalities and/or in case of increased cardiac troponin I values.

Perioperative Management of β-blocker Treatment

As administration of preoperative β-blocker use was not randomly assigned in this study, the exact time between β-blockers introduction and surgery was not known. However, each patient was evaluated by an anesthesiologist at least 10 days before surgery and the use of β-blockers was determined at this time. Patients taking β-blockers at the time of their preoperative evaluation continued to take them until surgery and were considered to be in the β-blocker group. Patients who were not taking β-blockers at the time of their preoperative evaluation were not given the drug in the interim and were considered to be in the non-β-blockers group.

Perioperative Bleeding Stratification

During the study period the transfusion rules were standardized. Patients with hemoglobin below 10g/dL were always compensated first by a transfusion of treated blood (Cell Saver®; Hemonetics™, Braintree, MA) from the surgical suction and by packed erythrocytes if required. Considering that packed erythrocytes is equivalent to a cup of treated blood (rounded mean of treated blood in a cup was 250 ± 20 ml), we defined a perioperative bleeding scale, based on transfused units, by adding the packed erythrocytes and the retransfused cup of treated blood. This provided us with a better approach to account for perioperative bleeding, than a scale based only on the number of packed erythrocytes used.

In order to explore the treatment effect of β-blockers according to the perioperative bleeding, we *a priori* defined three stratum of bleeding: normal bleeding (less than 5 cups of treated blood and/or packed erythrocytes), increased bleeding (between 5 and 10 transfused units), and major bleeding (more than 10 cups of treated blood and/or packed erythrocytes).

Endpoint Definition

Mortality was defined as death from any cause occurring during hospitalization or death within 30 days after surgery. After hospital discharge, all patients were evaluated between postoperative day 30 and day 45.

Three cardiac-related endpoints were defined:

(1) Postoperative myocardial necrosis defined as an abnormal cardiac troponin I value at any time during the postoperative period; the cutoff values used during the study period to define normality were 0.2 and 0.15 ng/ml, corresponding to the 99th percentile for our laboratory during each study period.[22]

(2) Postoperative myocardial infarction defined as a postoperative myocardial necrosis associated with symptoms of ischemia and/or electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block) and/or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[23]

(3) Cardiac death was defined by an expert committee where all observed deaths were classified by three experts blinded for the perioperative use of β-blockers as definite cardiac death, probable cardiac death, and noncardiac death.

Two noncardiac but vascular endpoints were also considered:

(1) Postoperative acute kidney injury defined as an increase of 30% in the postoperative serum creatinine concentration;

(2) Postoperative stroke defined by the occurrence of postoperative confirmed clinical neurologic deficit. Cerebral imaging was systematically used to confirm the clinical diagnosis.

Finally, two nonvascular endpoints were defined:

(1) Postoperative pneumonia defined as a body temperature more than 38°C; infiltrate on chest x-ray film; leukocytosis (more than 12,000 cells/mm^{-3}); microorganism isolated in bronchial secretions using protected mini bronchoalveolar lavage; and a threshold of 10^3 colony-forming units/ml, as described previously.[24] If pathogenic bacteria were not isolated, all other criteria were necessary for the diagnosis of pneumonia; alternatively, only two criteria were required;

(2) Multiple Organ Dysfunction Syndrome (MODS), previously known as multiple organ failure, was defined as the presence of two or more altered organ functions requiring intervention.[25]

Statistical Analysis

Data are expressed as mean ± SD and median (95% CI) for variables that are not normally distributed (normality was assessed with the D'Agostino–Pearson omnibus test), or number (percentage). Comparisons of means were performed using Student t test. Comparisons of proportions were performed using Fisher exact test.

The effect of preoperative chronic β-blocker therapy was assessed by propensity scores using boosted regression trees.[26,27] This consists of a linear combination of many trees, combined in the boosting framework in such a way that this combination can capture main effects and can produce a smooth fit. This approach is recognized to be an improvement over the more traditional logistic regression approach.[28] Patients were assigned to a propensity score that reflected the probability that they would receive chronic β-blocker therapy. The discriminative power of each model was quantified by calculating the area under the receiver operating characteristic curve (c-statistic).[29]

After propensity score estimate, the patients were analyzed by introducing the inverse probability of treatment weighting in logistic models.[30] This generates a pseudopopulation in which each covariate combination is balanced between the two groups. Weighting with inverse probability of received treatment allows for a population-based interpretation of results, as if the study population would have undergone a randomized trial in which, counter to fact, both treatments were applied to each subject. Standardized differences were used to assess the balance between groups.[31] Standardized difference

(d) is defined to be equal to $d = \dfrac{100 \cdot (\overline{X}_{treatment} - \overline{X}_{control})}{\sqrt{\dfrac{s^2_{treatment} + s^2_{control}}{2}}}$,

where $\overline{X}_{treatment}$, $\overline{X}_{control}$ are the mean values for the treatment and control groups, whereas $s^2_{treatment}$, $s^2_{control}$ are the sample variances respectively. An absolute standardized
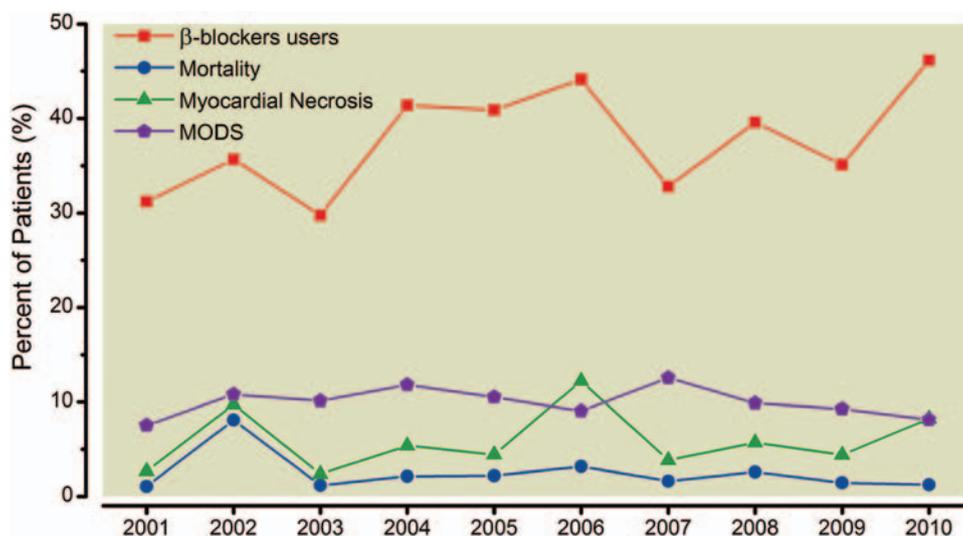

Fig. 1. Frequencies of the postoperative complications and of β-blocker users, according to the year of the surgery. No significant difference was retrieved. MODS = multiple organ dysfunction syndrome.

Table 1. Patient Characteristics

—	Unadjusted Comparisons				Adjustment with the Propensity Score			
—	Preoperative β Blockers (n = 675)	No Preoperative β Blockers, (n = 1,126)	Absolute Standardized Difference	P Value	Preoperative β Blockers (n = 675)	No Preoperative β Blockers (n = 1,126)	Absolute Standardized Difference	P Value
Demographic characteristics								
Age (year)	67 ± 11	68 ± 10	11.3%	0.03	67 ± 11	68 ± 10	3.3%	0.63
Sex	88%	88%	0.6%	0.89	88%	88%	2.8%	0.63
Medical history								
Myocardial infarction	33%	10%	48.5%	<0.001	33%	29%	7.8%	0.25
Coronary revascularization	14%	5%	24.0%	<0.001	14%	13%	1.2%	0.86
Coronary artery disease	60%	22%	79.0%	<0.001	60%	58%	5.4%	0.37
Heart failure	11%	3%	24.0%	<0.001	11%	10%	2.4%	0.74
Hypertension	80%	52%	71.4%	<0.001	80%	79%	2.7%	0.67
Chronic obstructive pulmonary disease	29%	34%	11.3%	0.02	29%	29%	1.3%	0.83
Pulmonary failure	7%	10%	11.4%	0.03	7%	7%	2.6%	0.61
Cirrhosis	0%	0%	7.7%	0.23	0%	0%	3.0%	0.59
Renal failure	21%	12%	20.8%	<0.001	21%	21%	1.7%	0.80
Preoperative hemodialysis	3%	1%	9.8%	0.02	3%	2%	2.1%	0.97
Diabetes	16%	14%	6.3%	0.24	16%	16%	0.3%	0.81
Revised cardiac risk index stratification								
Mean value ± SD	2.1 ± 0.8	1.5 ± 0.7	68.5%	<0.001	2.1 ± 0.8	2.0 ± 0.9	4.4%	0.52
Preoperative medications								
Angiotensin-converting enzyme inhibitors	38%	25%	27.2%	<0.001	38%	38%	0.2%	0.98
Statins	69%	46%	48.3%	<0.001	69%	67%	3.3%	0.58
Nitrates	12%	7%	17.0%	<0.001	12%	13%	1.6%	0.81
Calcium-channel blockers	32%	30%	5.4%	0.27	32%	35%	6.4%	0.30

Values are mean ± standard deviation or number (%).

difference above 10–15% was considered to represent meaningful imbalance.

A proportional Venn diagram has been used to quantify the distribution of postoperative pneumonia, postoperative myocardial infarction, and surgical complications in relation to in-hospital mortality.

Because of the exploratory nature of the study, we have made no adjustment for multiple testing. All P values are two-tailed, and $P < 0.05$ was considered to denote significant differences. Statistical analysis was performed with R (version 2.10).††

Results

Between January 2001 and December 2010, 1,803 patients were scheduled for abdominal aortic reconstruction. Two patients had incomplete records and were thus not included, leaving 1,801 patients for analysis, 677 (37.5%) of whom were treated preoperatively with β-blockers. The frequency of the perioperative use of β-blockers, MODS, severe bleeding, postoperative myocardial necrosis, postoperative myocardial infarction, and mortality according to year of surgery did not vary significantly over time (fig. 1). Association between chronic β-blocker therapy and patient characteristics are reported in table 1. Several imbalances were observed between the treatment and control groups, suggesting that chronic β-blocker therapy was used in association with other cardiovascular medications (angiotensin-converting enzyme inhibitors, statins, nitrates, calcium-channel blockers, and diuretics) in cardiac patients (history of coronary artery disease). It prompted the need for adjustment to produce unbiased conclusions regarding the association between chronic β-blocker therapy and postoperative outcome.

The model used to estimate the propensity score included all the variables reported in table 1. After propensity score

†† http://www.r-project.org. Accessed December, 28, 2011.

Table 2. Postoperative Adverse Events According to Preoperative Use of β-Blockers

—	β-Blockers User Group (n = 675)	Control Group (n = 1,126)	Univariate Analysis, P Value	Propensity Score Analysis		
—				OR	95% CI	P Value
Mortality	28 (4.1%)	17 (1.5%)	<0.001	1.83	(0.92; 3.72)	0.09
Cardiac mortality	14 (2.1%)	6 (0.5%)	0.01	2.69	(0.96; 8.51)	0.07
Myocardial infarction	26 (3.9%)	42 (3.7%)	0.90	0.46	(0.26; 0.80)	0.006
Mycardial necrosis	69 (10.2%)	111 (9.9%)	0.81	0.62	(0.43; 0.88)	0.009
Renal failure	94 (13.9%)	88 (7.8%)	<0.001	1.54	(1.08; 2.20)	0.02
Stroke	7 (1.0%)	2 (0.2%)	0.03	1.36	(0.30; 9.60)	0.71
MODS	67 (10.0%)	31 (2.8%)	<0.001	2.78	(1.71; 4.61)	<0.001
Pneumonia	88 (13.0%)	131 (11.6%)	0.41	0.91	(0.65; 1.22)	0.59
Any complication	184 (27.3%)	271 (24.1%)	0.14	0.91	(0.68; 1.13)	0.48

P values were not adjusted for multiple comparisons.
MODS = multiple organ dysfunction syndrome; OR = odds ratio.

adjustment (c-statistic, 0.88), no significant imbalance was observed in the patients' characteristics (table 1). The values of the propensity score in the treated patients (median: 0.60, 0.06–0.93) overlapped those of the untreated patients (median: 0.23, 0.03–0.85). Table 2 depicts the association of preoperative β-blocker use with the predefined endpoints in all patients. The effect of preoperative β-blocker use on mortality, postoperative myocardial necrosis, and MODS, according to RCRI, is depicted in figure 2. The use of RCRI to stratify the patients did not allow us to detect subgroups of patients with different effects of perioperative β-blockers. Analysis of predefined bleeding stratification (fig. 3) showed significant different effects regarding the amount of perioperative bleeding. In the normal bleeding group perioperative use of β-blockers appeared to be associated with a significant reduction of the frequency of postoperative myocardial necrosis (OR: 0.55 [0.29; 0.96]), whereas no significant association was observed in the other groups. In the increased bleeding group, the association between postoperative myocardial necrosis and β-blockers was no longer observed (OR: 0.58 [0.32; 1.02]), whereas the frequency of MODS was increased (OR: 2.46 [1.21; 5.08]). In the major bleeding group, perioperative β-blocker use was associated with increased mortality (OR: 6.65 [1.09; 129]), and increased frequency of MODS (OR: 4.18[1.81; 10.38]). The weight of this group (9% of the patients) impacted upon the global effect of perioperative use of β-blockers in this population of major vascular surgery, where a reduction in the frequency of postoperative myocardial necrosis was observed (table 2), but associated with an increased frequency of MODS (table 2). No significant association was observed with mortality in the entire population (table 2).

The relationship of postoperative adverse events to in-hospital mortality can be demonstrated in a proportional Venn diagram (fig. 4). Postoperative myocardial infarction was identified in only 13 (28%) of the observed deaths, suggesting these events were not implied in most of
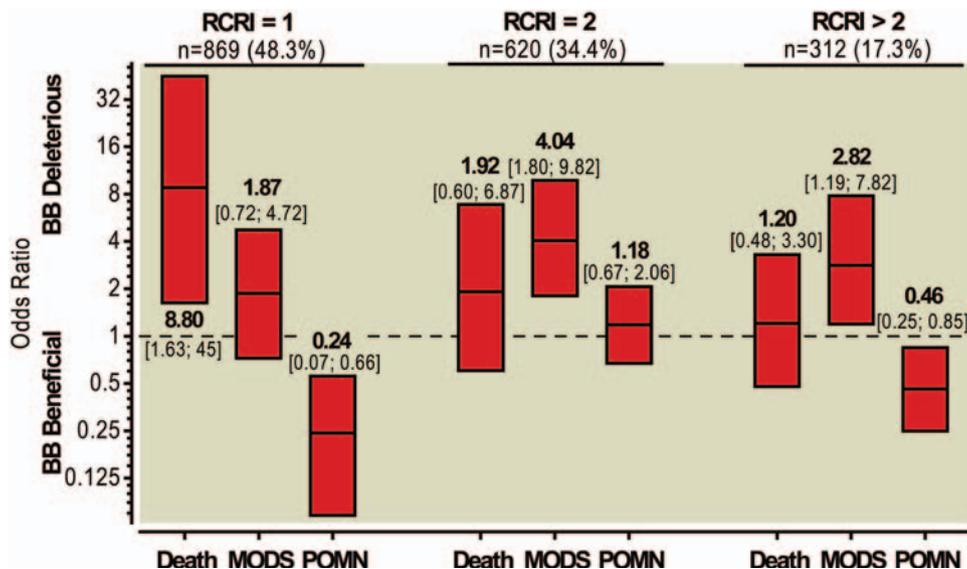
Fig. 2. Odds ratio (OR) associated with the β-blockers' (BB) use and multiple organ dysfunction syndrome (MODS), postoperative myocardial necrosis (POMN), or in-hospital mortality, according to the revised cardiac risk index (RCRI).
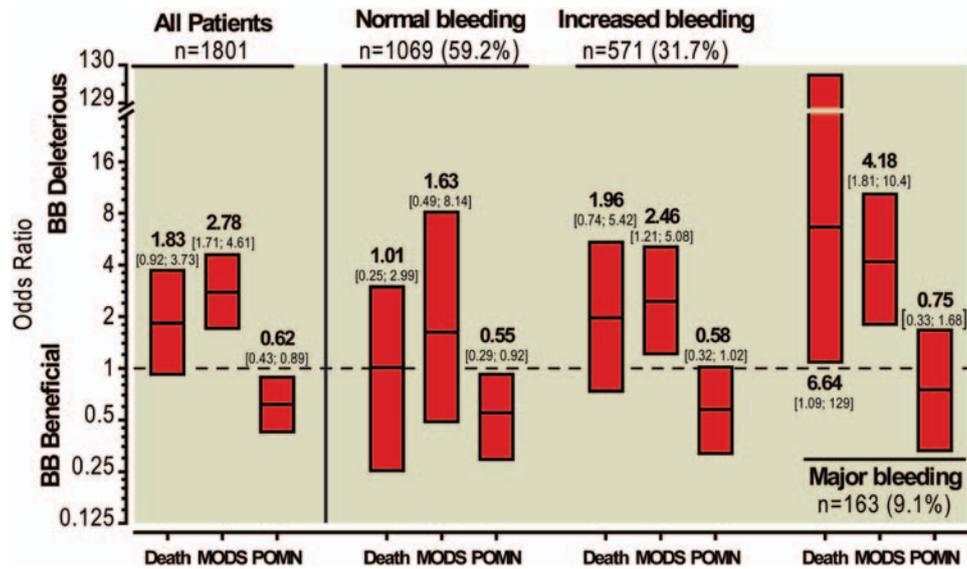
Fig. 3. Odd ratio (OR) associated with the β-blockers' (BB) use and multiple organ dysfunction syndrome (MODS), postoperative myocardial necrosis (POMN), or in-hospital mortality, according to the perioperative bleeding stratification.

postoperative deaths. Furthermore, surgical complications were observed in 45 (70%) of the patients presenting with a postoperative myocardial infarction. Finally, in-hospital deaths observed with postoperative myocardial infarction but without any others postoperative events was observed in only one patient (2% of the deaths, less than 0.1% of all patients)

Discussion

This study suggests that β-blockers are associated with a reduced frequency of postoperative cardiac events, but only when perioperative bleeding was limited. This

Fig. 4. Proportional Venn diagram representing the interrelation of postoperative pneumonia, postoperative myocardial infarction, and surgical complications in relation to in-hospital mortality. In-hospital mortality was 2.7%. All surfaces presented in this diagram are proportional to the numbers of patients observed in each subgroup.

study also demonstrates that in the case of excessive bleeding, β-blockers were associated with increased mortality, probably related to the observed increase in the frequency of postoperative MODS, and failed to prevent from myocardial necrosis. Two groups of this major vascular surgery population should be considered. A first group (normal bleeding, 59% of the patients), in which β-blockers were associated with reduced frequency of cardiac events and no significant difference in mortality or MODS, and a second group (major bleeding: 9% of the patients) where no significant association between use of β-blockers observed for all cardiac endpoints, but where a large increase in MODS and mortality was observed.

The magnitude of the effects observed in this study, protective or harmful, should not be neglected. We describe here a biphasic compound for the effects of β-blockers with clear protective effects for some patients and with clear harmful effects for the others. In order to have a clinically useful impact, we would need to be able to predict these severe bleedings during the preoperative period. Unfortunately, there are currently no tools to accurately predict these events. However, this study identified that β-blockers were associated with increased frequencies of adverse endpoints in this population where severe bleeding represented 10% of the patients. This observation suggests that the protective effects of β-blockers on postoperative cardiac events might balance more effectively their harmful effects in surgeries, where severe bleeding is not frequent (*e.g.*, orthopedic surgery).

The relationship between the postoperative complications remains difficult to summarize, but there is evidence to suggest that the surgical complications are associated with postoperative cardiac complications. Because surgical complications are observed before the diagnosis of all cardiac complications, this suggests that surgical complications might facilitate the postoperative adverse cardiac events.
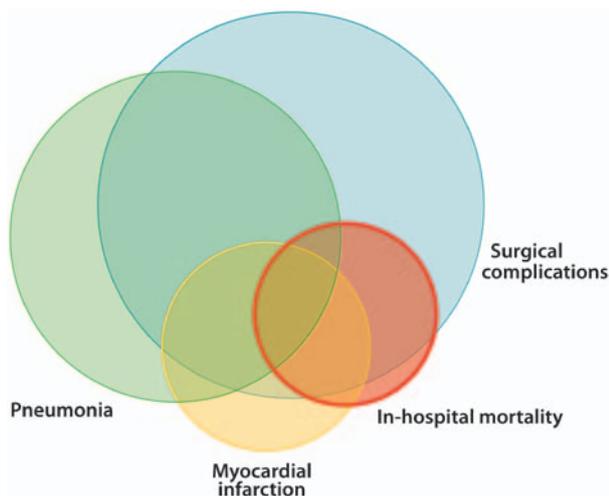
This hypothesis is supported by physiologic effects of anemia and/or hypovolemia on coronary events.

Therapeutic strategies aiming to preserve cardiac output and oxygen transport in critically ill patients are well described.[32] During anemia and hypovolemia, β-blockers limit the physiologic increase in cardiac output, which could produce some protective effects by reducing the oxygen intake from the myocardium, but also reduces the perfusion of other organs, and might induce adverse events linked to organ hypoperfusion.

In a previous study we evaluated the impact of preoperative statin therapy in major perioperative adverse events, and observed that statins did not present similar effects compared with those observed with β-blockers.[33] Thus, our results suggest that in surgical patients, if statins could be considered as beneficial whatever the occurrence of hemorrhagic complications, conversely, β-blockers should be considered differently as presented above. The described biphasic effects of β-blockers related to the hemorrhagic complications require the description of surgery associated with frequent hemorrhagic complications, in order to define the cases where the global effects of β-blockers might be deleterious.

Other approaches should be considered, including the use of short-acting β-blockers that could be titrated in case of hemorrhagic complications. Furthermore, other molecules such as ivabradine[34] seems to exert less impact upon cardiac function.[35] Nevertheless, their cardioprotective effects during the perioperative period need to be demonstrated.

Physiologic considerations suggest that hemoglobin requirement might be increased in patients with β-blockers, because the increase of cardiac output during hypovolemic anemia might be a concern for them.

Comparison with Other Studies

Beattie *et al.*[16] have not observed the previously described cardiac protective of β-blockers in their analysis. By stratifying per operative amounts of bleeding, we demonstrated the specific nature of the relationship between bleeding and β-blockers' cardiac effects in major vascular surgery. But, since we were not able to find any significant relationship with the postoperative hemoglobin nadir (measured 1 h after the end of surgery), we hypothesized that postoperative hemoglobin nadir was not a good indicator of intraoperative blood loss in major vascular surgery because of the early strategies of blood transfusion and given the kinetics of blood losses. The complete kinetics of hemoglobin measurements (including intraoperative measurements) was not available in this study. The second major difference between the two studies was the transfusion trigger, which was higher in our study and might have impacted the results.

Limitations

In this study, we have included patients undergoing major vascular surgery, and we have defined an empirical

stratification of bleeding based on our clinical day-to-day practice. These events are generally less frequent in other types of surgery. We expect that the observed results should be less marked in less hemorrhagic surgeries.

β-blockers were analyzed as a group of molecules; we have not considered differences between molecules or doses preoperatively used by the patients, because these data were not available. Nevertheless, no patients presented with bradycardia or hypotension. Of note, most β-blockers were already used for weeks by the patients. This point might have reduced the observed protective effect of β-blockers, as well as the noncardiac complications.

A specific limitation about the results for stroke have to be taken into account, because all patients were screened (Doppler) for carotid stenosis before surgery, and surgical carotid endarteriectomy was performed if required before aortic surgery. This might have reduce the frequency of the postoperative stroke.

Although several endpoints were considered, we did not adjust our results to correct for multiple comparisons and thus our findings should be interpreted with appropriate caution.

As with any evaluation of observational data, the foremost limitation is that we presume that all biases and confounding have been adjusted for in the model, an assumption that cannot truly be tested outside of a randomized study. Nevertheless, an experimental design would not be feasible regarding the hypothesis tested in this study, and because of current inability to predict severe bleeding at the time of inclusion, or before the abdominal aortic surgery.

Conclusions

The use of preoperative β-blockers was associated with a reduced frequency of postoperative cardiac events (myocardial necrosis or myocardial infarction) in patients undergoing major vascular surgery. Nevertheless, use was also associated with an increased frequency of postoperative MODS and a trend to increased in-hospital mortality. This effect, observed on all patients, seems to be linked to the marked increase in these adverse events in patients with severe peroperative bleeding, suggesting the deleterious effects of perioperative β-blockers in case of major bleeding.

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