THE PERIOPERATIVE USE OF ß-BLOCKERS

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Perioperative myocardial infarction is a leading cause of postoperative morbidity and mortality (1). The etiology of postoperative MI is the subject of some debate but is thought to include prolonged ischemia resulting from tachycardia (2).

Perioperative blockade could prevent perioperative cardiac damage and improve long-term cardiac outcome in noncardiac surgical patients. The beneficial effects of ß-blockers on myocardial function have been widely described (3). Beta-blockers reduce myocardial oxygen consumption by decreasing heart rate and extending the time of diastole, allowing better coronary perfusion. Furthermore, they attenuate the excitotoxic effects of catecholamines (4).

The American College of Cardiology and American Heart Association guidelines on perioperative assessment recommend perioperative blockers for noncardiac surgery. The most marked effects are observed in high-risk patients undergoing vascular surgery.

In cardiac surgery, the efficacy of ß-blockers is limited to the prevention of postoperative atrial fibrillation in coronary artery bypass graft (CABG) surgery, and only one observational analysis suggested a small but consistent survival benefit for patients receiving ß-blocker therapy and undergoing CABG surgery (5).

Beta-adrenergic antagonists bind selectively to the b-adrenoceptors producing a competitive and reversible antagonism of the effects of ß-adrenergic stimuli on various organs (Table 1). Their pharmacological effects can be explained from the knowledge of the responses elicited by these receptors in the various tissues and the activity of the sympathetic tone. Thus, ß-blockers

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have relatively little effect on heart rate and contractility in an individual at rest but slow heart rate and decrease cardiac contractility when the sympathetic nervous system is activated, i.e. during exercise or stress (6).

### Table 1: Effects mediated by $\beta_1$- and $\beta_2$-adrenoceptors

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Increase in heart rate</td>
<td></td>
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<tr>
<td>AV node</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Increase in conduction velocity</td>
<td></td>
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<tr>
<td>Atrioventricular node</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Increase in contractility</td>
<td></td>
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<tr>
<td>Ventricles</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Increase in contractility, conduction velocity and automaticity of idioventricular pacemakers</td>
<td></td>
</tr>
<tr>
<td>Arteries</td>
<td>$\beta_1$</td>
<td>Vasodilation</td>
<td></td>
</tr>
<tr>
<td>Veins</td>
<td>$\beta_2$</td>
<td>Vasodilation</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>$\beta_1$</td>
<td>Vasodilation, increased contractility, $K^+$ uptake</td>
<td></td>
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<tr>
<td>Liver</td>
<td>$\beta_1$</td>
<td>Glycogenolysis and gluconeogenesis</td>
<td></td>
</tr>
<tr>
<td>Pancreas (β-cells)</td>
<td>$\beta_1$</td>
<td>Insulin and glucagon secretion</td>
<td></td>
</tr>
<tr>
<td>Fat cells</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Lipolysis</td>
<td></td>
</tr>
<tr>
<td>Bronchi</td>
<td>$\beta_2$</td>
<td>Bronchodilation</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Renin release</td>
<td></td>
</tr>
<tr>
<td>Gallbladder and ducts</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder detrusor</td>
<td>$\beta_2$</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Uterus</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Relaxation</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal nerve terminals</td>
<td>$\beta_2$</td>
<td>Promotes noradrenaline release</td>
<td></td>
</tr>
<tr>
<td>Parathyroid glands</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Parathyroid hormone secretion</td>
<td></td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>$\beta_2$</td>
<td>$T_4 \rightarrow T_3$ conversion</td>
<td></td>
</tr>
</tbody>
</table>

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The indications of $\beta$-blockers were as follows:

- Hypertension
- Prophylaxis of stable angina attacks
- Tachyarrhythmias
- After AMI treatment and prophylaxis (secondary prophylaxis)
- Hyperthyroidism
- Hypertrophic obstructive cardiomyopathy
- Chronic congestive heart failure
- Migraine
- Pheochromocytoma
- Glaucoma
- Panic and anxiety
- Portal hypertension

The contraindications to initiate $\beta$-blocker treatment include asthma, symptomatic hypotension or bradycardia and severe decompensated heart failure. Contraindications may be relative, in patients in whom the benefit of therapy may outweigh the risk of untoward effects. Chronic obstructive lung disease without bronchospastic activity and peripheral vascular disease...
are not considered as absolute contraindications and high risk patients may obtain a significant benefit from this therapy. Patients with heart failure and bradycardia due to sick sinus node or second or third degree AV-block may benefit from pre-treatment with pacemaker in order to tolerate β-blockers, although this approach has, however, not been formally tested. Diabetes or intermittent lower limb claudication are not absolute contraindications for β-blockers use.

**Review of major randomized controlled trials of perioperative β-blockade**

The McSPI group trial included Veterans Affairs (VA) patients with, or at risk for, CAD undergoing non-cardiac surgery. Atenolol was used as the study drug. The primary outcome was all-cause mortality at 6 months and 1 and 2 yr with a secondary outcome of combined MI, unstable angina, congestive heart failure (CHF), myocardial revascularization, and/or death. The study showed significant benefits in both the primary and secondary endpoints. At 2 yr follow-up, mortality was significantly lower in the atenolol group (10% vs 21% in the placebo group) with a reduction in the incidence of postoperative cardiac events (7).

The first DECREASE trial examined patients with positive results on dobutamine stress echocardiography undergoing major vascular surgery. Patients were randomized to either standard perioperative treatment or bisoprolol. The study showed a significant reduction in its primary endpoint of composite death from cardiac causes or nonfatal MI within 30 days after operation (34% in the Standard care group vs 3.4% in the bisoprolol group) (8).

The POBBLE (Perioperative β-Blockade) trial was a randomized double-blinded placebo-controlled trial of metoprolol in patients without CAD undergoing infrarenal vascular surgery under general anaesthesia. Hospital stay was shorter in the metoprolol arm (10 compared with 12 days; P,0.02). More patients in the metoprolol group required intraoperative inotropic support (9).

In DIPOM, diabetic patients undergoing major non-cardiac surgery received sustained-release metoprolol 100 mg per day or placebo starting the day before surgery, continuing after operation to a maximum of 8 days. The mean duration of postoperative metoprolol or placebo intervention was 4.6 and 4.9 days, respectively. The primary outcome was composite of all-cause mortality, AMI, unstable angina, or CHF. However, they did find a significant increase in hypotension and bradycardia in the treatment group (10).

Metoprolol after Vascular Surgery (MaVS) was a double blinded randomized placebo-controlled trial did not show any clear benefit to perioperative b-blockade in vascular surgery patients, who were previously presumed to
benefit from this therapy (11).

The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study was a double
blinded placebo-controlled multicentre trial evaluating the cardiovascular
protective effects of 10 days of oral bisoprolol in patients having spinal
anaesthesia (12).

POISE included 8351 patients with or at risk of atherosclerotic disease
randomized to placebo or metoprolol succinate extended release (ER) 100
mg orally. The primary endpoint of the POISE trial mirrored other trials with
a composite of cardiovascular death, non-fatal MI, and non-fatal cardiac
arrest at 30 days. Metoprolol reduced the primary endpoint A significant de-
crease in MI was largely responsible for the overall reduction in the primary
endpoint. However, there was a significant increase in total mortality in the
metoprolol group. Stroke incidence was 1% with metoprolol compared with
0.5% (13).

Esmolol

Esmolol is an ultra–short-acting ß-blocker, with a plasma half-life of app-
proximately 2 minutes, a time to peak effect of about 6 to 10 minutes after
administration, and a washout time considered to be 9 minutes after stop-
ning infusion. All these properties suggest using this ß-blocker as the first-
choice drug in critical patients in whom possible side effects such as cardiac
failure, hypotension, or bradycardia cause a rapid and immediate interrup-
tion of drug administration. Usually, it is used as a loading dose followed by
a continuous infusion. These clinically useful pharmacologic characteristics
have led to the use of esmolol in the prevention of a sympathetic response
in cardiac surgery.

The meta-analysis of Zangrillo et al. in 2009 showed that ultra–short-
acting ß-blocker esmolol is probably the best choice of alpha-blocker in the
perioperative period of patients undergoing cardiac surgery. In the studies
included in the present meta-analysis, esmolol was used in 3 different cli-
nical conditions: (1) preventing the hemodynamic response to some pro-
cedures (in particular extubation), (2) treatment and prophylaxis of atrial
fibrillation at the end of CPB, and (3) administration during surgery (in many
cases just before and during the cardioplegia) in order to reach or improve
myocardial protection. Numerous studies showed how an increase of tachy-
cardia is strongly connected to episodes of myocardial ischemia (14).

Another meta-analysis about esmolol use in non-cardiac surgery conclu-
ded that esmolol seemed to reduce the incidence of myocardial ischemia
in non-cardiac surgery without increasing the episodes of hypotension and
bradycardia (15).
To conclude:
- β-blockers are protective against cardiac complications in high risk surgery
- the high and fixed doses of β-blockers may be harmful due to its hypotensive effect
- esmolol reduces the incidence of myocardial ischemia and arrhythmias in cardiac surgery
- esmolol reduces myocardial ischemia in non-cardiac surgery without increasing the episodes of hypotension and bradycardia
- the important issue about β-blockers is titration.

REFERENCES: