REVIEW ARTICLE

Possible indications of beta-blockers in the perioperative period other than prevention of cardiac ischemia

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Abstract According to the guidelines of the American College of Cardiology/American Heart Association 2006 for perioperative cardiovascular evaluation for non-cardiac surgery, beta-blocker therapy should be considered for high-risk individuals undergoing vascular surgery or high- and intermediate-risk patients undergoing non-cardiac surgery. This guideline might induce physicians to increasingly use beta-blockers in the hope of preventing perioperative cardiac complications. However, beta-blockers have potential beneficial effects outside the prevention of cardiac events. In addition to reducing anesthetic and analgesic requirements during the perioperative period, beta-blockers have neuroprotective effects in patients with brain trauma and possible effectiveness in the management of intraoperative awareness-induced post-traumatic stress disorder. Moreover, intrathecal administration of beta-blockers may have antinociceptive effects. Physicians need to bear in mind the benefits of beta-blockers for purposes other than preventing cardiac events when applied in the perioperative period, and they should be familiar with the pharmacodynamics and risk–benefit ratio with their use. This review focuses on possible extracardiac indications of beta-blockers.

Keywords Anesthetic requirements · Beta-blockers · Immunomodulation · Intraoperative

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Introduction

Beta-blocker therapy is widely known to reduce perioperative cardiovascular complications [1, 2]. Recent guidelines from the American College of Cardiology/American Heart Association [2] recommend the use of beta-blockers in high-risk patients undergoing vascular surgery or high- and intermediate-risk patients undergoing non-cardiac surgery. While this guideline might induce physicians to increasingly use beta-blockers during surgery in the hope of preventing perioperative cardiac events, beta-blockers have potential beneficial effects in addition to the prevention of cardiac events. This review focuses on the possible extracardiac indications of beta blocker therapy.

All beta-blockers are able to antagonize the transduction of the beta-adrenergic receptor signal. Currently used beta-blockers can be roughly classified into four divisions depending on their ancillary properties, namely, intrinsic sympathomimetic activity, beta-receptor subtype specificity (beta 1 vs. beta 2), and membrane-stabilizing activity, respectively. Prichard's classification is widely accepted for classifying the known beta-blockers. This classification is summarized in Table 1 [3].

Beta-blockers reduce anesthetic and analgesic requirements during the perioperative period

Reduction of anesthetic requirements

Studies carried out during the last 20 years have revealed that the perioperative use of beta-blockers can decrease anesthetic requirements [4–15].

Stanley et al. [8] were the first to report the possible beneficial effects of perioperative use of beta-blockers on

Table 1 Characteristics of clinically used beta-blockers, Prichard classification

Division	Group	Drug	Beta-1/beta-2 selectivity Propranolol = 1	ISA	MSA	Main metabolic organ	Other activity
I	1	Alprenolol	1	++	+	Hepatic/renal	
	2	Propranolol	1	−	+	Hepatic	Inverse agonist
	3	Pindolol	15–20	+++	−	Hepatic/renal	
		Carteolol	5–15	++	−	Hepatic/renal	
	4	Nadolol	5	−	−	Hepatic/renal	
II	1	Acebutolol	0.1	+	+	Hepatic/renal	
	2	Celiprolol	0.1–0.3	+	−	Hepatic = renal	Beta 2-agonist
	4	Metoprolol	0.8–1.0	−	−	Hepatic	Inverse agonist
		Atenolol	1	−	−	Renal	
III	1	Labetalol	0.3	+/−	+	Renal/hepatic	
	2	Carvedilol	3–5	−	+	Hepatic	Antioxidant alpha 1-antagonist
	4	Amosulalol	0.25	−	−	Hepatic/renal	
		Arotinolol	5	−	−	Hepatic/renal	
IV		Nipradilol	3	−	−	Hepatic = renal	

ISA intrinsic sympathomimetic activity, *MSA* membrane stabilizing effect

+, Effect present; −, effect absent

the reduction of anesthetic dosage. They compared the dose of sufentanil required to produce unconsciousness during anesthetic induction in 22 patients receiving propranolol (80–240 mg/day, oral doses) and 22 patients not receiving propranolol or any other beta-blocker therapy prior to coronary artery bypass grafting (CABG). The variables compared between the two groups were incidence of intraoperative hypertension, requirements for supplements to treat hypertension, and recovery times. Patients on propranolol therapy required an average of 3.8 ± 0.3 μg/kg of sufentanil to reach unconsciousness, while patients not taking any beta-adrenergic blockers needed 4.9 ± 0.3 μg/kg of sufentanil. Total intraoperative sufentanil dose requirements were 11.1 ± 0.8 μg/kg for patients on propranolol and 15.0 ± 1.0 μg/kg for patients not taking any beta-blockers. In addition, systolic blood pressure increases of >20% the preoperative (control) values during sternotomy and maximal sternal spread occurred significantly more frequently in patients not taking beta-blockers than in those administered propranolol. Of the patients not taking beta-blockers, 18 and 27% required phentolamine to control arterial blood pressure before bypass and during the bypass, respectively. In contrast, only 5% of patients on propranolol therapy needed phentolamine before bypass, none of required it during bypass. Stanley et al. speculated that the possible mechanisms by which propranolol could potentiate the effects of sufentanil include increased occupation of the opiate receptor sites of the central nervous system (CNS), stimulation of CNS opiate receptors, reduction of plasma volume, changes in the distribution

volume of sufentanil, decreased sufentanil metabolism, or alteration of CNS membranes, resulting in increased transfer of sufentanil into the brain.

In 1991, Smith et al. [9] compared esmolol, a short-acting beta-1 blocker, with alfentanil as a supplement for propofol–nitrous oxide–atracurium anesthesia. These researchers showed that esmolol can be used in place of alfentanil to supplement propofol–nitrous oxide–atracurium anesthesia in outpatients undergoing arthroscopic procedures, although esmolol-treated patients required more postoperative pain relief and opioid analgesia than those treated using alfentanil. Johansen et al. [7] subsequently examined in detail whether esmolol could reduce the propofol concentration required to prevent movement at skin incision. Patients were anesthetized with propofol alone, propofol plus low-dose continuous esmolol infusion (bolus of 0.5 mg/kg, maintenance dose of 50 μg/kg/min), or propofol plus high-dose continuous esmolol infusion (bolus 1 mg/kg, maintenance dose of 250 μg/kg/min) along with 60% nitrous oxide. The esmolol infusion was initiated before the induction of anesthesia and continued until the completion of the study. The researchers were able to show that the high-dose esmolol infusion induced a 26% reduction in the minimum effective plasma concentration (CP50; defined as suppression of movement at incision in 50% of patients) of propofol with nitrous oxide. This led them to conclude that esmolol may have anesthetic-sparing effects in humans under clinically relevant conditions. They also found that the minimum alveolar concentration (MAC) of isoflurane was not altered when esmolol was used alone but

that it was significantly decreased while high doses of es-molol was used with alfentanil [6]. These data indicate that esmolol does not have anesthetic effects per se, rather, it has anesthetic-sparing effects when used in conjunction with anesthetic agents. Johansen [10] examined whether esmolol affected the electroencephalogram (EEG) during propofol/alfentanil anesthesia and found that bispectral index (BIS) was significantly suppressed and that the burst suppression ratio (SR) was increased by esmolol (BIS 37 ± 6–22 ± 6, 40% decrease; SR 5 ± 7 to 67 ± 23, 13.4-fold increase) compared with baseline levels. In addition, discontinuation of esmolol reversed these changes in BIS and SR values.

A study by Zaugg et al. [5] examined the effects of atenolol administration on hemodynamic stability, adequacy of anesthetic depth, anesthetic and analgesic requirements, and recovery from anesthesia. Patients were assigned to receive either pre- and postoperative atenolol or intraoperative atenolol. They demonstrated that although perioperative beta-blockade did not significantly alter the hormonal stress response, beta-blocked patients showed improved hemodynamic stability both during emergence from anesthesia and postoperatively. In addition, patients treated with atenolol perioperatively required less isoflurane than patients without atenolol perioperatively, and patients who received intra- or pre-and postoperative atenolol required less fentanyl than patients without any beta-blockers. Further, despite the differences in intraoperative anesthetic dose requirements in this study, the depths of anesthesia, as indicated by average BIS values, were similar in all three groups. Patients treated with atenolol had significantly shorter recovery times and were discharged from the post-anesthetic care unit (PACU) earlier. Total morphine doses and pain scores in the PACU were also lower in patients treated with atenolol. Zaugg et al. subsequently performed a post-hoc analysis of the administration of atenolol during the perioperative period, and re-confirmed that atenolol reduces anesthetic requirements but does not modify anesthetic depth indicators [13]. Other investigators [11, 12, 14–17] have shown the efficacy of esmolol in reducing anesthetic requirements without affecting BIS (Table 2). For example, a recent study by Collard et al. [17] examined the effects of a continuous infusion of esmolol (5–15 µg/kg/min) in the absence of opioid supplements during surgery. In this study, the control group received intermittent doses of fentanyl, the esmolol group received a continuous infusion of esmolol with no supplemental opioids intraoperatively, and the remifentanil group received a continuous infusion of remifentanil (0.1–0.5 µg/kg/min). These researchers found that fentanyl requirements in the PACU were significantly lower in the esmolol group (91.5 ± 42.7 µg) as compared with the other two groups (remifentanil: 237.8 ± 54.7 µg,

control: 168.1 ± 96.8 µg). Nausea was more frequent in the control (66.7%) and remifentanil (67.9%) groups than in the esmolol group (30%). The esmolol group left the hospital 45–60 min earlier.

In contrast, using dogs, Tanifuji and Eger [18] examined the effects of propranolol on anesthetic requirements, specifically changes in the MAC of halothane, accompanying acute [2 and 10 mg/kg intravenous (iv)] and chronic (200 mg/day orally for 10 days) propranolol administration and found no effect of acute or chronic propranolol administration on halothane MAC. In addition, they demonstrated that an intravenous beta-agonist, isoproterenol also had no effect on MAC. These researchers suggested that since propranolol readily crosses the blood–brain barrier (BBB), neither acute inhibition of central beta-adrenergic receptors nor chronic receptor blockade with potential changes in central catecholamine levels influence volatile anesthetic MAC. Orme et al. [19] examined the effects of esmolol on propofol concentration and the prevention of response to command and found no effects of the use of esmolol on anesthetic requirements during propofol anesthesia. Larson et al. [20] examined whether esmolol infusion (intravenous bolus of 1.5 mg/kg of esmolol, followed by an infusion at 100 µg/kg/min) would blunt pupillary changes in response to noxious stimulation and found that esmolol infusion did not blunt such changes.

Landiolol (ONO 1101) is a newly developed, highly ultra-short-acting beta-1 blocker created by altering the chemical structure of esmolol [21–23]. This agent is approximately ninefold more potent in beta-1 blocking activity and eightfold more cardioselective than esmolol. The suppressive effects of landiolol on cardiovascular performance have been reported to be less potent than those of esmolol at equipotent beta-blocker doses [23]. Landiolol exhibits suppression predominantly on the chronotropic effect, rather than on the inotropic effect. Thus, landiolol is suitable for stabilizing hemodynamics during the perioperative period. There have, however, been a few studies on the anesthetic-sparing effect of landiolol during anesthesia [24–27]. Kurita et al. [26], using a swine model, examined the effects of landiolol on the MAC of isoflurane required to prevent movement in response to a noxious stimulus in 50% of the experimental animals. A landiolol infusion was administered at a rate of 0.125 mg/kg/min for 1 min and thereafter decreased to 0.04 mg/kg/min. The results showed that landiolol attenuated the increases in heart rate and mean arterial blood pressure that occurred in response to the dewclaw clamp, but they did not alter the MAC of isoflurane. In contrast, Tanabe et al. [25] showed that a low dose of landiolol (bolus injection of 0.031 mg/kg and continuous infusion at a rate of 0.01 mg/kg/min) reduces intraoperative

Table 2 Study characteristics of effects of beta-blockers on anesthetic requirements

Author	Subjects	Treatment	Main results
Beneficial effects			
Stanley et al. [7]	22 CABG patients	80–240 mg per day of propranolol	Lower requirement of sufentanil during surgery
Smith et al. [8]	97 outpatients	2 mg/kg of esmolol infusion	No difference in hemodynamic variables between esmolol and alfentanil group
Johansen et al. [6]	60 patients	Bolus 1 mg/kg, then 250 µg/kg/min of esmolol infusion	Lower propofol requirement
Johansen et al. [5]	100 patients	Bolus 1 mg/kg, then 250 µg/kg/min of esmolol infusion	Decrease in MAC of isoflurane
Zaugg et al. [4]	63 patients	Intra or pre- and postoperative atenolol treatment	Lower fentanyl requirement during surgery and morphine dosage in the PACU
Coloma et al. [10]	53 outpatients	Esmolol infusion(12.8 ± 13.1 µg/kg/min) during surgery	Use of esmolol as an alternative to remifentanil
Menigaux et al. [11]	50 patients	Bolus 1 mg/kg, followed by 250 µg/kg/min of esmolol infusion during induction	Attenuated somatic response to tracheal intubation prevented BIS arousal reactions
Berkenstadt et al. [13]	30 patients	Single dose of 80 mg of esmolol	No affect on BIS value
Wilson et al. [14]	60 patients	Bolus 1 mg/kg, followed by 250 µg/kg/min of esmolol infusion during induction	Reduction of propofol requirements for anesthetic induction by 25%
Ghosh et al. [15]	90 patients	Metoprolol 100 mg for 1 h prior to surgery	Reduction of total dose of propofol required during surgery
Collard et al. [16]	90 patients	Bolus of 1 mg/kg, followed by 5–15 µg/kg/min of esmolol infusion during surgery	Reduction of fentanyl requirements in PACU
Tanabe et al. [24]	25 patients	Bolus of 0.031 mg/kg, followed by 0.01 mg/kg/min of landiolol infusion during surgery	Reduction of sevoflurane requirement during operation
No effects			
Tanifuji et al. [17]	In dogs	2 and 10 mg/kg intravenous or 200 mg/day for 10 days of propranolol	No effect on halothane MAC
Larson et al. [19]	13 volunteers	Bolus of 1.5 mg/kg, followed by 100 µg/kg/min of esmolol infusion during surgery	No effect of esmolol on the pupillary response
Orme et al. [18]	30 patients	Bolus 1 mg/kg, followed by 5–15 µg/kg/min of esmolol infusion during surgery	No effect on anesthetic requirement of propofol
Kurita et al. [25]	In swine	Bolus of 0.125 mg/kg, followed by 0.04 mg/kg/min of landiolol	No effect on isoflurane MAC

CABG Coronary artery bypass grafting, BIS bispectral index, PACU post-anesthetic care unit, MAC minimum alveolar concentration

sevoflurane requirements during sevoflurane/N$_2$O/fentanyl anesthesia in patients undergoing hip surgery.

One important question that emerged during the investigations of these anesthetic-sparing effects of beta-blockers was whether beta-blockers mask the signs of light anesthesia and thus increase intraoperative awareness [28]. Ginsburg [29], in 1992, initially posed the question, "is IV esmolol an acceptable substitute for an inadequate anesthetic?" Since then, many studies have shown the efficacy of using beta-blockers in reducing anesthetic requirements during the perioperative period without any change in anesthetic depth [4–15]. Studies showing reduced anesthetic requirements by esmolol have mainly been based on BIS. This raises the important issue of whether BIS is a valid predictor of anesthetic depth. "Inadequate" anesthesia can cover several different levels, ranging from implicit memory, explicit memory, and obeying commands during anesthesia without recall, to actual awareness and recall [30]. The proper definition of "inadequate anesthesia" is thus of great importance in addressing this issue.

Beta-blockers seem likely to have no anesthetic effect per se, as reported by Johansen et al. [6]. The mechanisms underlying the effects of esmolol on anesthetic requirements remain unclear. One possible explanation may be that beta-blockers have CNS-modulating activities and exert anxiolytic effects (see following section). Another explanation may lie in an alteration of propofol pharmacokinetics by beta-blockers. Upton et al. [31] demonstrated that cardiac output is a determinant of the initial concentrations of propofol after the administration of short infusions. A reduction in cardiac output leads to reduced hepatic blood flow, which could affect the metabolism of drugs with a large hepatic extraction ratio, such as fentanyl. Beta-blocker use would thus likely result in the prolongation of the analgesic effects of fentanyl and also elicit a reduction in postoperative opioid consumption. Indeed, Kurita et al. [24] suggest that the pharmacodynamic changes and pharmacokinetic modifications of anesthetic agents induced by the decrease in cardiac output resulting from the administration of beta blockers should contribute to an anesthetic-sparing effect during anesthesia.

Major questions still exist about the mechanisms and sites of anesthetic action. Classically, it has been widely assumed that the brain, especially the cerebral cortex, is the main site of anesthetic action. Anesthetic effect may result in the several components of general anesthesia: unconsciousness, amnesia, and immobility in response to a painful stimulus. The standard for determining anesthetic requirements is the MAC of an inhaled agent that prevents gross purposeful movement in response to a supramaximal painful stimulus. Antognini et al. [32] demonstrated, in animal studies, the importance of subcortical structures, such as the spinal cord, in the generation of purposeful

movement in response to a painful stimulus under general anesthesia. Laboratory studies [33, 34] have shown that it is of great interest that the mechanisms and sites of action of beta-blockers used for reducing anesthetic requirements during surgery may be closely related to the site of anesthetic action. In addition, the measurement and assessment of anesthetic potency, such as MAC, is also of great interest during investigations of the effect of beta-blockers on the reduction of anesthetic requirements. Rampil et al. [34] found that anesthetic-induced unresponsiveness to noxious stimuli measured by MAC testing did not depend on cortical forebrain structures in rats. These researchers therefore speculated that beta-blockers administered during the perioperative period may exert their anesthetic-sparing effects, not by effects on the cerebral cortex, but via the spinal cord.

Antinociceptive effects

Involvement of the sympathetic system in nociception is well established. Some reports have indicated that beta-blockers may produce antinociceptive effects. Davidson et al. [35] examined the effects of esmolol infusion on nociceptive behaviors induced by the formalin test in rats. Esmolol infused at low (40 mg/kg/h) and high (150 mg/kg/h) doses did not affect behavioral changes recorded immediately after formalin injection (phase 1; 0–5 min), whereas only the high dose was effective in decreasing limb lifting during the secondary response (phase 2; 10–35 min). Taira et al. [36] subsequently examined the effects of intrathecal landiolol on nociceptive behaviors in the rat formalin test. Intrathecal injection of landiolol was found to decrease the number of flinches in a dose-dependent manner, with the effect induced by 0.5 mg of landiolol being completely reversed by intrathecal isoproterenol. These researchers concluded that beta-blockers may have antinociceptive effects. Kinjo et al. [37] subsequently reported almost the same finding. Zhao et al. [38] recently examined the effects of administering intrathecal landiolol on nociception and spinal c-Fos expression by the mouse formalin test. The intrathecal injection of 750 μg/kg landiolol decreased pain-related behaviors in phase 1 (the initial acute phase: during the first 5 min after formalin injection followed by a prolonged tonic response), while intrathecal landiolol administered at 250, 500 and 750 μg/kg decreased pain-related behaviors in phase 2 (secondary and longer lasting response: beginning about 10 min after formalin injection) during the formalin test. c-Fos protein levels in the spinal dorsal horn were decreased by landiolol administered at 750 μg/kg. In a human study, Zaugg et al. [5] reported that the intravenous administration of atenolol pre-and postoperatively or during surgery resulted in lower pain scores and reduced the total morphine requirement in

the PACU. Chia et al. [39] reported that patients treated with esmolol infusion during hysterectomy required less patient-controlled intravenous morphine over 3 days than those not administered esmolol, despite similar pain intensity and medication side effects, and they also received significantly lower concentrations of end-tidal isoflurane and fentanyl during anesthesia.

The mechanisms of beta-blocker-induced antinociceptive effects remain unclear. Tanahashi et al. [40] showed that propranolol, esmolol, landiolol, and lidocaine block tetrodotoxin-resistant Na channels in rat spinal dorsal root ganglia in a dose-dependent manner, although very high landiolol concentrations are required to achieve antinociceptive effects.

Noxious stimuli are conducted through the spinal cord, the brainstem reticular formation, and the thalamus to the cerebral cortex, where an electroencephalographic arousal response is evoked [41, 42]. Beta-adrenoceptors are present in various parts of the reticular activating system, particularly the medial septal region of the basal forebrain. In mice and rats, the locus coeruleus-associated noradrenergic system participates in arousal, and beta-blockers within this region reduce forebrain electroencephalographic activity [41, 42]. In a continuation of these studies, the same group of researchers [43] showed that amphetamine-induced activation of the rat forebrain is clearly inhibited by timolol. Radisavievic et al. [44] found that norepinephrine modulated excitatory amino acid-induced responses in developing human and adult rat cerebral cortexes. These findings strongly suggest the contribution of beta-adrenergic mechanisms to antinociception via a central site. However, the pharmacokinetics of beta-blockers, particularly esmolol, do not entirely support this mechanism. Esmolol is hydrophilic, as is atenolol. They produce the same plasma/cerebrospinal fluid ratio, and probably do not readily cross the BBB. However, Johansen [10] found that esmolol promoted electroencephalographic burst suppression during propofol/alfentanil anesthesia. Howie et al. [45] and Van den Broek et al. [46] showed that esmolol reduced the duration of seizures induced by electroconvulsive therapy (ECT). These reports suggest that esmolol may cross the BBB. In contrast, another study showed that esmolol had no effect on seizure duration [47]. Given these contradictory results, the question of whether esmolol or atenolol can cross the BBB remains unanswered.

Another potential mechanism of the antinociceptive effects of beta-blockers is via their action on peripheral anti-inflammatory sites [48–52]. The results from a study using human subjects revealed that norepinephrine increases hyperalgesia in response to heat in skin-sensitized by capsaicin [48]. In addition, Khasar et al. [49] showed that epinephrine produced cutaneous mechanical hyperalgesia and sensitized cultured dorsal root ganglion neurons in the absence of nerve injury via beta-adrenergic receptors and that these effects of epinephrine were mediated by both the protein kinase A and protein kinase C second-messenger pathways. Cunha et al. [51] reported that carrageenin-evoked hyperalgesia was attenuated by atenolol. Ernberg et al. [52] reported that injection of propranolol into the human masseter muscle reduces the pain induced by local administration of 5-HT.

Although extensive data from both experimental and clinical studies have shown that beta-blockers may have antinociceptive effects, the body of evidence is as yet insufficient to conclusively state that beta-blocker therapy is effective in blocking nociceptive stimuli. Further extensive experimental and clinical studies are needed to clarify the antinociceptive mechanisms of beta-blockers.

Central nervous system effects

Many studies have demonstrated that beta-blockers affect the CNS [53–67]. Ko et al. [53] reviewed the association of beta-blockers used in the treatment of myocardial infarction, heart failure, or hypertension with depression, fatigue, and sexual dysfunction, and showed that although the frequency of depressive symptoms was similar between subjects using beta-blockers (20.1%) and placebo (20.5%), the frequency of fatigue and sexual dysfunction symptoms was higher in the those using beta-blockers (fatigue: 33.4 vs. 30.4%, respectively; sexual dysfunction: 21.6 vs. 17.4%, respectively). The side effects of the use of beta-blockers, such as depressive symptoms or increased frequency of fatigue, clearly suggest that beta-blockers affect the CNS. Brismar et al. [54, 62] examined the relationship between beta-blocker-induced CNS side effects and the nightly urinary secretion of melatonin in hypertensive patients. They found that severe CNS side-effects, such as nightmares and sleep disorders, occurred only in patients treated with metoprolol (21%) and that these side-effects were always accompanied by low levels of melatonin. Kostis and Rosen [55] showed that beta-blockers can affect rapid eye movement (REM) sleep, possibly associated with nightmares. Yamada et al. [61] indicated that beta-adrenergic receptor occupation is related to sleep disorders. Another study showed that lipophilic beta-blockers have a relatively greater effect on sleep disorders [65].

The administration of moderate doses of the catecholamines epinephrine and norepinephrine shortly after memory training is known to result in the enhancement of later retention performance [57, 58]. Nielson and Jensen [60] compared the effects of beta-blockers on arousal-induced modulation of working memory between elderly and young humans. The young subjects, normal elderly subjects, and those taking no beta-blocker medications all showed

enhanced long-term recognition performance as a result of arousal manipulation; in contrast, elderly patients with beta-blockers exhibited impaired arousal-induced modulation of working memory.

Although the effects of beta-blockers on the CNS, such as sleep disorders or memory impairment, may not be beneficial to surgical patients, Pitman et al. [68] undertook a pilot study to determine whether the administration of propranolol shortly after a traumatic event can prevent post-traumatic stress disorder (PTSD), thereby demonstrating that the acute post-traumatic administration of propranolol may have preventive effects on subsequent PTSD. The symptoms of PTSD resemble—and have been suggested to result from—the psychiatric sequelae of some degree of intraoperative awareness [69], so that the intraoperative use of beta-blockers may also prove effective in the management of intraoperative awareness-induced PTSD. Pitman stated that "The body releases epinephrine and other stress hormones during a trauma, probably as part of a survival mechanism. Epinephrine helps you cope in the traumatic situation, but also makes the memory of the situation stronger. Interrupting beta-adrenergic transmission during or immediately after trauma with propranolol can block the emotional potentiation of memory and forestall PTSD" [68].

Neuroprotective effects are another possible beneficial effect of beta-blockers on the CNS [70–77]. In animal studies, Lysko et al. [70] examined the neuroprotective mechanisms underlying the effects of carvedilol on cultured cerebellar neurons and on CA1 hippocampal neurons in gerbils exposed to brain ischemia. These researchers found that carvedilol protected cultured neurons in a dose-dependent manner against both glutamate-mediated excitotoxicity and oxidant stress. They concluded that carvedilol may reduce the risk of cerebral ischemia and stroke by virtue of both antihypertensive actions and antioxidant properties. Savitz et al. [71] subsequently demonstrated that carvedilol was neuroprotective in focal cerebral ischemia and may protect the ischemic brain by inhibiting apoptosis and attenuating the expression of tumor necrosis factor (TNF)-alpha and interleukin (IL)-1 beta. Little et al. [78] examined the effects of propranolol on cerebral blood flow and early ischemic changes following middle cerebral artery (MCA) occlusion in cats. Propranolol was infused at a rate of 1 mg/kg/h for 4 h, beginning 1 h before MCA occlusion, and a 4 mg/kg bolus was administered immediately before occlusion. These researchers found that although the changes in cerebral blood flow and EEG in the propranolol-treated cats were not different from those in propranolol-untreated cats, there were significant decreases in infarct volume in propranolol-treated cats relative to propranolol-untreated cats. The same group subsequently showed the beneficial effects of propranolol in acute focal cerebral ischemia [79]. In contrast, Junker et al. [80] showed that clenbuterol induces neuroprotective effects via an increase in nerve growth factor expression and that this beneficial effect is blocked by propranolol. Goyagi et al. [81, 82] recently examined the neuroprotective effects of several beta-blockers in rats with transient focal cerebral ischemia. The rats received an intravenous infusion of saline, propranolol, carvedilol, esmolol, and landiolol 30 min before MCA occlusion, and the infusion was continued for 42 h. Cerebral infarct volumes in the cortex were lower in rats treated with propranolol (72 ± 33 mm^3), carvedilol (64 ± 25 mm^3), esmolol (65 ± 18 mm^3), and landiolol (44 ± 18 mm^3) than in saline-treated rats (205 ± 28 mm^3).

A number of clinical studies have demonstrated beta-blocker exposure with reduced mortality in patients with head injury [72–77]. Inaba et al. [73] retrospectively evaluated 1156 patients with isolated head injury who were admitted to the Intensive Care Unit during a 90-month period. Of these, 203 (18%) received beta-blockers and 953 (82%) did not. Although patients receiving beta-blockers had severe head injury more frequently, had lower Glasgow Coma Scale scores, and more frequently required craniotomy, beta-blocker use was an independent protective factor for mortality (odds ratio 0.54, 95% confidential interval 0.33–0.91). Other investigators have reported almost the same results [74–77]. In addition, Amory et al. [72] retrospectively examined the perioperative use of beta-blockers on neurological complications in patients undergoing coronary artery bypass graft surgery and showed that the use of beta-blockers was associated with a substantial reduction in the incidence of postoperative neurological complications. These reports indicate that beta-blockers may exert neuroprotective effects when used in the perioperative period. Further extensive investigations are needed to verify these potentially important neuroprotective effects.

Immune response and beta-adrenergic antagonists

Activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, resulting in a systemic release of adrenal steroid hormones and catecholamines, is a well-known essential component of the response to major surgery, brain injury, or trauma. The balance of pro-and anti-inflammatory cytokines may be altered perioperatively. These changes are thought to be attributable to the stress response of surgery or the response to cardiopulmonary bypass. An important consequence of the pro-inflammatory cytokine activity is increased adhesion of neutrophils. Further, high levels of these stress mediators are known to be immunosuppressive in surgical patients.

Some reports have shown that beta-blockers may have immunomodulatory effects during cerebral injury [83–89] or myocardial infarction [90, 91]. Prass et al. [83] investigated the effects of propranolol on the immunoinhibitory alterations induced by stroke. Their study showed that the administration of propranolol to animals with middle cerebral artery occlusion decreased the percentage of apoptotic splenocytes to levels observed in sham-operated mice and prevented decreases in peripheral blood lymphocyte counts. Another study [88] showed that propranolol prevented an increase in IL-10 plasma levels in a rat model of acute brain injury. Carvedilol increases the production of IL-12 and interferon-alpha [86] and decreases the production of TNF-alpha and IL-6 [84]. Atenolol reportedly decreases the production of TNF-alpha [87]. Katafuchi et al. [89] demonstrated that reduction in natural killer cytotoxicity produced by stimulation of the splenic nerve was completely blocked by the intravenous administration of nadolol (a peripherally acting beta-blocker), but not by infusion of prazosin (an alpha-antagonist).

With respect to the effects of beta-blockers on the immunomodulatory system during myocardial infarction, there have been some reports on the effects of beta-blockers on the inflammatory system [90–92]. Prabhu et al. [92] demonstrated the efficacy of metoprolol treatment in reducing the production of TNF-alpha and IL-1 beta protein in rat myocardial infarction models. Other studies [90, 91, 93] have also shown the effects of metoprolol or carvedilol on cytokine production in patients with myocardial infarction. Loiek et al. [94] reported that carvedilol prevents the increased production of reactive oxygen species in HL-60 cells.

In contrast, Lang et al. [95] reported that the continuous infusion of propranolol in septic rats exacerbated the sepsis-induced increase in skeletal muscle IL-6 and TNF-alpha protein. Schmitz et al. [96] reported that the administration of propranolol (0.5 mg/kg subcutaneous every 12 h) in septic mice increased the splenocyte apoptosis rate, reduced the proliferative capacity of splenocytes, and modulated cellular cytokine release (IL-6 and interferon-gamma), resulting in an increase in sepsis-induced lethality from 47 up to 68%. However, in a clinical study, Jeschke et al. [97] demonstrated that propranolol not only decreased serum TNF and IL-1 beta levels compared with controls but that it also attenuated the incidence of sepsis in severely burned children. These reports may indicate that the effects of beta-blockers depend on the immunomodulatory condition of the animal before administration of the drug, as suggested by Oberbeck [98]. It is interesting that Benish et al. [99] found that the combination of a COX-2 inhibitor and a beta-blocker (etodolac and propranolol) attenuated surgery-induced decreases in natural killer

cytotoxicity, suggesting a possible reduction in the risk of tumor metastasis.

Although there is as yet no laboratory or clinical evidence supporting the suggestion that the perioperative use of beta-blockers would be able to modulate the immune–endocrine system, when the effects of anesthetic agents on the immune–endocrine system [100] are considered together with the results of these experimental studies, the perioperative use of beta-blockers may plausibly modulate the immunosuppressive alterations induced by surgical stress.

Other considerations

Effects of beta-blockers on pulmonary function

There have been some reports on the effects of beta-blockers on pulmonary function [101–103]. Although patients with active asthma should not receive beta-blockers, chronic obstructive pulmonary disease is not a contraindication to the use of beta-blockers perioperatively, and even patients with inactive stable asthmatic disease may be given a low dose of highly selective beta-1 blockers, such as landiolol. While the single-dose administration of beta-agonists produces bronchodilation and inhibits airway hyperresponsiveness, chronic repetitive administration may increase airway hyperresponsiveness, airway inflammation, and the risk of death. It is interesting to note that Nquyen et al. [101] demonstrated that chronic administration of beta-blockers reduced inflammation and mucous metaplasia in a murine model of asthma.

Another possible beneficial effect of beta-blockers on pulmonary function is that beta-blockers enhance hypoxic pulmonary vasoconstriction [102, 103], which may be favorable in patients undergoing one-lung ventilation.

Use of short-acting beta-blockers during intubation or emergence periods

Laryngoscopy and tracheal intubation maneuvers induce marked hemodynamic changes, such as increases in heart rate and systolic blood pressure, which, in combination, result in an unfavorable supply–demand balance of myocardial oxygen. The degree of response to laryngeal stimulation appears to vary with the depth of anesthesia [104], the duration [105] and difficulties encountered during tracheal intubation [106, 107], as well as on patient-dependent variables, including age and history of diabetes or cardiovascular disease [108, 109]. Although the hemodynamic changes are transient, drastic hemodynamic changes in patients with pre-existing ischemic coronary disease, hypertension or cerebrovascular disease may increase the

risk of myocardial ischemia, arrhythmia, and even infarction and cerebral hemorrhage [110, 111].

To date, many studies have shown the effectiveness of esmolol in blunting the hemodynamic changes induced by endotracheal intubation. Figueredo and Garcia-Fuentes [112] provided an excellent review of the effectiveness of different regimes and doses of esmolol, as well as the grade of hypotension and bradycardia that can be produced when esmolol is used in conjunction with anesthesia-inducing agents. Of the 72 publications they identified, 38 randomized controlled trials containing a total of 2009 patients were ultimately included in their analysis. Following anesthetic induction, systolic blood pressure values decreased (with respect to baseline) by 6.1% in placebo groups and by 13.8% in esmolol-treated patients. Following endotracheal intubation, systolic blood pressure increased by 26.3% in patients in the placebo group compared with an increase of 9.1% in patients treated with the various regimes of esmolol. After induction of anesthesia, minimum heart rates for the placebo group were 7.2% higher than baseline values, while those for the esmolol group were 4.2% lower than baseline values. Endotracheal intubation resulted in a 29.6% increase in the heart rate of patients in the placebo group compared with a 9.3% increase in patients treated with esmolol. These researchers concluded that, with respect to the administration of esmolol "before" or "after" administration of the induction agents, no significant differences were observed between the two alternatives with respect to any of the variables assessed. They also concluded that esmolol is effective in blocking the tachycardia and systolic blood pressure increase induced by airway manipulation. However, the use of esmolol is associated with a dose-dependent risk of hypotension during the induction of anesthesia, thereby precluding its routine use in anesthesia. The use of esmolol in specific risk groups remains controversial, and in groups in whom the risk–benefit ratio is difficult to predict, usage needs to be evaluated on an individual basis. To diminish the incidence and seriousness of the side-effects, a reasonable recommendation is to administer a small loading dose (500 µg/kg) of esmolol over 4 min, followed by a continuous intravenous infusion of 200–300 µg/kg/min.

In contrast to the use of esmolol to prevent hemodynamic changes during endotracheal intubation, few studies have examined the effects of landiolol on hemodynamic changes associated with endotracheal intubation [113–117]. Kitamura et al. [115] examined the dose-related effects of landiolol on cardiovascular responses to tracheal intubation and found that although the administration of 0.25 and 0.5 mg/kg landiolol decreased the incidence of tachycardia, these doses were insufficient to suppress increases in systolic blood pressure. Hasuo et al. [116] examined the effects of a continuous infusion of landiolol on hemodynamic responses to endotracheal intubation during induction with isoflurane. Landiolol was infused at a rate of 0.125 mg/kg/min for 1 min as a loading dose, followed by a maintenance dose of 0.04 mg/kg/min. These researchers found that significant increases in heart rate occurred in both the control and landiolol groups in response to isoflurane inhalation and tracheal intubation, although the magnitude of the increase was significantly reduced in the landiolol group. Blood pressure increased after tracheal intubation in the control group but remained unchanged in the landiolol group. Plasma concentrations of norepinephrine increased after induction and intubation in both groups, with no significant differences between groups. Only one study has compared the effects of esmolol and landiolol on hemodynamic responses to endotracheal intubation: Oda et al. [118] examined the comparative effects of esmolol and landiolol on hemodynamic changes and BIS during anesthesia induction. Esmolol was administered as a bolus of 1.0 mg/kg, followed by infusion at 0.25 mg/kg/min, while landiolol was given as a bolus of 0.125 mg/kg, followed by infusion at 0.04 mg/kg/min. The administration of these agents was started 5 min after the induction of anesthesia, and endotracheal intubation was performed 12 min after anesthetic induction. These researchers observed no significant differences in hemodynamic changes between esmolol and landiolol groups throughout the study periods. Sugiura et al. [119] examined the optimal dose of landiolol in terms of the hemodynamic alterations induced by laryngoscopy in normotensive and hypertensive patients. Landiolol at a dose of 0.1 mg/kg was the most effective against intubation-induced tachycardia when infused 4 min before intubation in normotensive patients. However, a 0.2 mg/kg dose of landiolol was necessary to prevent tachycardia after intubation in hypertensive patients. They concluded that landiolol had no significant effects on arterial blood pressure at any dose, indicating that landiolol is suitable for stabilizing hemodynamic changes during intubation.

Emergence from anesthesia and tracheal extubation are also associated with marked hemodynamic alterations, such as increases in heart rate and systolic blood pressure. Such changes may induce adverse effects in patients with ischemic heart disease. Physicians therefore need to be cognizant of whether ultra-short-acting drugs, such as esmolol or landiolol, provide hemodynamic stabilization during emergence from anesthesia and tracheal extubation. Some reports have examined the effects of esmolol on hemodynamic changes during the extubation period [120–123]. Dyson et al. [120] assessed the effects of three doses of esmolol (1.0, 1.5, and 2.0 mg/kg) given as a bolus 2 min after the reversal of neuromuscular blockade, in a double-blinded study, and found that all three doses of esmolol

attenuated increases in heart rate but that 1.0 mg/kg was insufficient to control increases in systolic blood pressure associated with emergence from anesthesia and tracheal extubation. They concluded that doses of 1.5 and 2.0 mg/kg controlled both systolic blood pressure and heart rate, but that the larger dose produced significant decreases in systolic blood pressure. Kurian et al. [121] examined whether esmolol infusion affected the incidence of ST-segment changes during tracheal extubation after coronary artery surgery. Esmolol was infused from the time of the patient's entry into the intensive care unit until 180 min after tracheal extubation, with the aim of maintaining heart rate within the range of 55–75 beats/min. A "sliding scale" of esmolol at 0–300 μg/kg/min was used, depending on heart rate. Patients in the esmolol group displayed a lower incidence of myocardial ischemia than those in the placebo group (3/31 vs. 12/37, $p = 0.05$). Although esmolol infusion stabilized the hemodynamic changes associated with extubation, seven patients in the esmolol group suffered adverse events related to esmolol infusion that were not found in the placebo group. These researchers therefore concluded that although the use of esmolol reduced the incidence of myocardial ischemia, the incidence of adverse effects makes this agent unsuitable for routine prophylaxis in patients after coronary artery surgery. Kovac et al. [122] compared the effectiveness of intravenous nicardipine (0.03 mg/kg) and esmolol (1.5 mg/kg) in controlling heart rate and blood pressure responses to emergence and extubation and found that although esmolol was more effective than nicardipine in attenuating heart rate responses to extubation, nicardipine was more effective in controlling blood pressure responses. An interesting study was performed by Grillo et al. [123] in which a 0.3 mg/kg/min infusion of esmolol was administered from the end of anesthesia to 15 min after extubation to patients undergoing neurosurgery. They found that esmolol blunted increases in cerebral blood flow velocity during emergence, an effect that may be attributable to hyperemia during neurosurgical recovery.

In contrast to esmolol, very few reports have examined the effects of landiolol on the hemodynamic changes of emergence from anesthesia and extubation [124–126]. Nonaka et al. [124] looked at the effects of continuous landiolol infusion on the hemodynamic changes of emergence. Landiolol was continuously infused at a rate of 0.125 mg/kg/min for 1 min immediately after the injection of neostigmine–atropine. The results demonstrated the efficacy of landiolol administration on hemodynamic stabilization during recovery from general anesthesia. Nakagawa et al. [125] reported a case demonstrating the usefulness of landiolol in the prevention of myocardial ischemia during extubation and recovery from anesthesia.

Specific points for attention

Metabolic effects of beta-blockers

Several studies have indicated that there is some hyperglycemic effect in patients treated with beta-blockers. Although the mechanism of beta-blocker-induced hyperglycemia is not clearly proven, it is reported that beta-blockers increase fasting glucose by as much as 28 mg/dl and glycosylated hemoglobin by 1% [127]. A recent large study [127] showed that beta-blockers impaired glucose tolerance and appeared to increase the risk of diabetes on a long-term basis by 28%. Another large study from Bakris et al. [128] compared the effects of carvedilol and metoprolol on glycemic control, showing that carvedilol stabilized glycosylated hemoglobin and improved insulin resistance compared with metoprolol. However, to date, there have been no reports describing the use of beta-blockers on glucose homeostasis during the perioperative period.

Another criticism of the use of beta-blockers is unfavorable changes in lipid metabolism [129], although this adverse effect is not of immediate concern in the perioperative period. Significant increases in mean plasma total and very-low-density lipoprotein cholesterol and reductions in high-density lipoprotein cholesterol and free fatty acids concentrations have been reported with the use of atenolol, metoprolol, propranolol, and oxprenolol.

Drug interactions

Concurrent administration of beta-blockers with drugs that alter gastrointestinal, hepatic, and renal function may affect the plasma concentrations, duration of action, and efficacy of beta-blockers.

It is widely known that the co-administration of calcium channel blockers with beta-blockers induces suppression of myocardial function, sinus arrest, or atrioventricular block. The review articles by Kjeldsen et al. [130] and Brouwer et al. [131] emphasize that although the clinical importance of the combined use of calcium channel blockers and beta-blockers on the treatment of angina pectoris in patients with coronary artery disease has been documented, careful attention should be paid to the concurrent use of calcium channel blockers with beta-blockers in the presence of impaired left ventricular function, bradycardia, or conduction abnormalities.

There have been a number of reports describing the possible interactions of beta-blockers and other agents. Westphal et al. [132] found an increased bioavailability of digoxin with oral co-administration of talinolol, resulting from competition for intestinal P-glycoprotein. Other reports show the possible interaction of beta-blockers and clonidine [133, 134].

Of great concern to anesthesiologists is a possible interaction between anesthetic agents and beta-blockers. Remifentanil and esmolol are metabolized by non-specific esterases and other tissues, which may alter the pharmacokinetics of remifentanil. However, laboratory studies in rats revealed no pharmacokinetic or pharmacodynamic interaction between remifentanil and esmolol in this animal model [135, 136].

Propofol may alter myocardial beta-adrenoceptor binding and responsiveness. However, Zhou et al. [137] demonstrated that relatively high concentrations of propofol were needed to antagonize beta-adrenoceptor binding and tissue responsiveness in the rat heart. Based on experimental studies, it has also been reported that volatile anesthetics can modify beta-adrenoceptor stimulations [138–140]. However, as yet, the interaction between propofol or volatile anesthetics and beta-blockers has not been clinically proven.

Conclusions

While beta-blockers have been widely used for hemodynamic stabilization during the perioperative period, they have a number of additional potential beneficial effects other than prevention of cardiac events, such as antinociceptive effects, reduced anesthetic dosage during the perioperative period and, possibly, immunomodulation. Physicians need to bear in mind the benefits of beta-blockers other than for preventing cardiac events when using these agents in the perioperative period, and they should be familiar with their pharmacodynamics and balance of risks and benefits when using them for these extra-cardiac beneficial effects.

References

1. London MJ, Zaugg M, Schaub MC, Spahn DR. Perioperative beta-adrenergic receptor blockade. Anesthesiology. 2004;100:170–5.
2. Fleisher LA, Beckman JA, Brown KA, Calkins H, Charikof EL, Fleischmann KE, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy. Circulation. 2006;113:2662–74.
3. Prichard BNC. Beta-adrenergic receptor blockade in hypertension, past, present and future. Br J Clin Pharmacol. 1978;5:379–99.
4. Zaugg M, Schaub MC, Pasch T, Spahn DR. Modulation of beta-adrenergic receptor subtype activities in perioperative medicine: mechanisms and sites of action. Br J Anaesth. 2002;88:101–23.
5. Zaugg M, Tagliente T, Lucchinetti E, Jacobs E, Krol M, Bodian C, et al. Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. Anesthesiology. 1999;91:1674–86.
6. Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. Anesth Analg. 1998;87:671–6.
7. Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. Anesthesiology. 1997;86:361–71.
8. Stanley TH, Lange SD, Boscoe MJ, Bruun ND. The influence of chronic preoperative propranolol therapy on cardiovascular dynamics and narcotic requirements during operation in patients with coronary artery disease. Can J Anaesth. 1982;29:319–24.
9. Smith I, Hemelrijck JV, White PF. Efficacy of esmolol versus alfentanil as a supplement to propofol–nitrous oxide anesthesia. Anesth Analg. 1991;73:540–6.
10. Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. Anesth Analg. 2001;93:1526–31.
11. Coloma M, Chu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. Anesth Analg. 2001;92:352–7.
12. Menigaux C, Guignard B, Adam F, Sessler DI, Joly V, Chauvin M. Esmolol prevents movement and attenuates the BIS response to orotracheal intubation. Br J Anaesth. 2002;89:857–62.
13. Zaugg M, Tagliente T, Silverstein JH, Lucchinetti E. Atenolol may not modify anesthetic depth indicators in elderly patients—a second look at the data. Can J Anaesth. 2003;50:638–42.
14. Berkenstadt H, Loebstein R, Faibishenko I, Halkin H, Keidan I, Perel A. Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anesthesia. Br J Anaesth. 2002;89:509–11.
15. Wilson ES, McKinlay S, Crawford JM, Robb HM. The influence of esmolol on the dose of propofol required for induction of anesthesia. Anaesthesia. 2004;59:122–6.
16. Ghosh I, Bithal PK, Dash HH, Chaturvedi A, Prabhakar H. Both clonidine and metoprolol modify anesthetic depth indicators and reduce intraoperative propofol requirement. J Anesth. 2008;22:131–4.
17. Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, et al. Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg. 2007;105:1255–62.
18. Tanifuji Y, Eger EI II. Effect of isoproterenol and propranolol on halothane MAC in dogs. Anesth Analg. 1976;55:383–7.
19. Orme R, Leslie K, Umranikar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. Anesth Analg. 2002;93:112–6.
20. Larson MD, Sessler DI, Washington DE, Merrifield BR, Hynson JA, McGuire J. Pupillary response to noxious stimulation during isoflurane and propofol anesthesia. Anesth Analg. 1993;76:1072–8.
21. Iguchi S, Iwamura H, Nishizaki M, Hayashi A, Senokuchi K, Kobayashi K, et al. Development of a highly cardioselective ultra-short-acting beta-blocker, ONO-1101. Chem Pharm Bull. 1992;40:1462–9.
22. Atarashi H, Kuruma A, Yashima M, Saitoh H, Ino T, Endoh Y, et al. Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias. Clin Pharmacol Ther. 2000;68:143–50.
23. Sasao J, Traver SD, Kindscher JD, Taneyama C, Benson KT, Goto H. In rabbits, landiolol, a new ultra-short-acting beta blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. Can J Anaesth. 2001;48:985–9.
24. Kurita T, Takata K, Morita K, Sato S. Lipophilic beta-adrenoceptor antagonist propranolol increases the hypnotic and anti-

nociceptive effects of isoflurane in a swine model. Br J Anaesth. 2008;100:841–5.

25. Tanabe T, Fukusaki M, Fujinaga A, Ando Y, Yamashita K, Terao Y, et al. Landiolol, a new ultra-short-acting beta 1-blocker, reduces anesthetic requirement during sevoflurane/N$_2$O/fentanyl anesthesia in surgical patients. Eur J Anaesthesiol. 2009;26:39–42.

26. Kurita T, Takata K, Uraoka M, Morita K, Sato S. Landiolol, an ultra-short-acting beta 1-adrenoceptor antagonist, does not alter the minimum alveolar anesthetic concentration of isoflurane in a swine model. Anesth Analg. 2007;105:656–60.

27. Kurita T, Morita K, Fukuda K, Takata K, Uraoka M, Sanjo Y, et al. Landiolol, an ultra-short-acting beta 1-adrenoceptor antagonist, dose not alter the electroencephalographic effect of isoflurane in swine model. Br J Anaesth. 2006;96:602–7.

28. Yang H, Fayad A. Are beta-blockers anesthetics? Can J Anaesth. 2003;50:627–30.

29. Ginsburg RS. Is intravenous esmolol an acceptable substitute for an inadequate anesthetic? Anesth Analg. 1982;74:76–777.

30. Rusell IF, Wang M. Absence of memory for intra-operative information during surgery with total intravenous anesthesia. Br J Anaesth. 2001;86:196–202.

31. Upton RN, Ludbrook GL, Grant C, Martinez AM. Cardiac output is a determinant of the initial concentrations of propofol after short infusion administration. Anesth Analg. 1999;89:545–52.

32. Antognini JF, Schwartz K. Exaggerated anesthetic requirements in the preferentially anesthetized brain. Anesthesiology. 1993;79:1244–9.

33. Borges M, Antognini JF. Does the brain influence somatic responses to noxious stimuli during isoflurane anesthesia? Anesthesiology. 1994;81:1511–5.

34. Rampil IJ, Mason P, Singh H. Anesthetic potency (MAC) is independent of forebrain structures in rats. Anesthesiology. 1993;78:707–12.

35. Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. Can J Anaesth. 2001;48:59–64.

36. Taira Y, Kakinohana M, Kakinohana O, Okuda Y. ONO 1101, a novel ultra-short acting beta-1 blocker, can reduce pain behaviour in the rat formalin test. Anesthesiology. 1998;89:A1128.

37. Kinjo S, Kakinohana M, Sugawara K. Esmolol and landiolol, ultra short acting beta-1 blockers can reduce pain behavior in the rat formalin test. Anesth Analg. 2005;100:S-265.

38. Zhao H, Sugawara T, Miura S, Iijima T, Kashimoto S. Intrathecal landiolol inhibits nociception and spinal c-Fos expression in the mouse formalin test. Can J Anaesth. 2007;54:201–7.

39. Chia YY, Chan MH, Ko NH, Liu K. Role of beta-blockade in anesthesia and postoperative pain management after hysterectomy. Br J Anaesth. 2004;93:799–805.

40. Tanahashi S, Iida H, Oda A, Osawa Y, Dohi S. Effect of beta-adrenoceptor antagonists on tetrodotoxin-resistant Na channels in rat dorsal root ganglion neurons. Anesthesiology. 2003;99:A–962.

41. Berridge CW, Foote SL. Enhancement of Behavioral and electroencephalographic indices of waking following stimulation of noradrenergic beta-receptors within the medial septal region of the basal forebrain. J Neurosci. 1996;16:6999–7009.

42. Berridge CW, White K. Contrasting effect of noradrenergic beta-receptor blockade within the median septal area on forebrain electroencephalographic and behavioral activity state in anesthetized and unanesthetized rat. Neuroscience. 2000;97:543–52.

43. Berridge CW, Morris MF. Amphetamine-induced activation of forebrain EEG is prevented by noradrenergic beta-receptor blockade in the halothane-anesthetized rat. Psychopharmacology (Berl). 2000;148:307–13.

44. Radisavievic Z, Cepeda C, Peacock W, Buchwald NA, Levine MS. Norepinephrine modulates excitatory amino acid-induced responses in developing human and adult rat cerebral cortex. Int J Dev Neurosci. 1994;12:353–61.

45. Howie MB, Bloack HA, Zvara D, McSweeney TD, Martin DJ, Coffman JA. Esmolol reduces automatic hypersensitivity and length of seizures induced by electroconvulsive therapy. Anesth Analg. 1990;71:384–8.

46. Van den Broek WW, Leentjens AFG, Mulder PGF, Kusuma A, Bruijn JA. Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study. Br J Anaesth. 1999;83:271–4.

47. Kovac AL, Goto H, Arakawa K. Esmolol bolus and infusion attenuates increases in blood pressure and heart rate during electroconvulsive therapy. Can J Anaesth. 1990;37:58–62.

48. Drummond PD. Noradrenaline increases hyperalgesia to heat in skin sensitized by capsaicin. Pain. 1995;60:311–5.

49. Khasar SG. Epinephrine produces a beta-adrenergic receptor-mediated mechanical hyperalgesia and in vitro sensitization of rat nociceptors. J Neurophysiol. 1999;81:1104–12.

50. Garabededian BS, Poole S, Haddad JJ, Massaad CA, Jabbur SJ, Saade NE. The role of the sympathetic efferents in endotoxin-induced localized inflammatory hyperalgesia and cytokine upregulation. Neuropharmacology. 2002;42:864–72.

51. Cunha FQ, Lorenzetti BB, Poole S, Ferreira SH. Interleukin-8 as a mediator of sympathetic pain. Br J Pharmacol. 1991;104:765–7.

52. Ernberg M, Lundeberg T, Kopp S. Effect of propranolol and granisetron on experimentally induced pain and allodynia/hyperalgesia b intramuscular injection of serotonin into the human masseter muscle. Pain. 2000;84:339–46.

53. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. JAMA. 2002;288:351–7.

54. Brismar K, Hylander B, Eliasson K, Rossner S, Wetterberg L. Melatonin secretion related to side-effects of beta-blockers from the central nervous system. Acta Med Scand. 1988;223:525–30.

55. Kostis JB, Rosen RC. Central nervous system effects of beta-adrenergic blocking drugs: the role of ancillary properties. Circulation. 1987;75:204–12.

56. Betts TA, Alford C. Beta-blockers and sleep: a controlled trial. Eur J Clin Pharmacol. 1985;28:65–8.

57. Van Stegeren AH, Everaerd W, Cahill L, McGaugh JL, Gooren LJG. Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. Psychopharmacology. 1998;138:305–10.

58. Przybyslawski J, Roullet P, Sara SJ. Attention of emotional and nonemotional memories after their reactivation: role of beta-adrenergic receptors. J Neurosci. 1999;19:6999–7009.

59. Gleiter CH, Deckert J. Adverse CNS-effects of beta-adrenoceptor blockers. Pharmacopsychiatry. 1996;29:201–11.

60. Nielson KA, Jensen RA. Beta-adrenergic receptor antagonist antihypertensive medications impair arousal-induced modulation of working memory in elderly humans. Behav Neural Biol. 1994;62:190–200.

61. Yamada Y, Shibuya F, Hamada J, Sawada Y, Iga T. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. J Pharmacokinet Biopharm. 1995;23:131–45.

62. Brismar K, Moqensen L, Wetterberq L. Depressed melatonin secretion in patients with nightmares due to beta-adrenoceptor blocking drugs. Acta Med Scand. 1987;221:155–8.

63. Thompson DF, Pierce DR. Drug-induced nightmares. Ann Pharmacother. 1999;33:93–8.

64. Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. Nature. 1994;371:702–4.

65. McAinsh J, Cruickshank JM. Beta-blockers and central nervous system side effects. Pharmacol Ther. 1990;46:163–97.

66. Kayed K, Godtlibsen OB. Central effects of the beta-adrenergic blocking agent acebutolol. A quantitative EEG study using normalized slope descriptors. Eur J Clin Pharmacol. 1997;12:327–31.

67. Kayed K, Godtlibsen OB. Effects of the beta-adrenoceptor antagonists acebutolol and metoprolol on sleep pattern in normal subjects. Eur J Clin Pharmacol. 1977;16:323–6.

68. Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, et al. Pilot study of secondary prevention of post-traumatic stress disorder with propranolol. Biol Psychiatry. 2002;51:189–92.

69. Larkin M. Can post-traumatic stress disorder be put on hold? Lancet. 1999;354:1008.

70. Lysko PG, Lysko KA, Yue TL, Webb CL, Gu JL, Feuerstein G. Neuroprotective effects of carvedilol, a new antihypertensive agent, in cultured rat cerebellar neurons and in gerbil global brain ischemia. Stroke. 1992;11:1630–5.

71. Savitz SI, Erhardt JA, Anthony JV, Gupta G, Li X, Barone FC, et al. The novel beta-blocker, carvedilol, provides neuroprotection in transient focal stroke. J Cereb Blood Flow Metab. 2000;8:1197–204.

72. Amory DW, Grigore A, Amory JK, Gerhardt MA, White WD, Smith PK, et al. Neuroprotection is associated with beta-adrenergic receptor antagonists during cardiac surgery: evidence from 2,575 patients. J Cardiothorac Vasc Anesth. 2002;16:270–7.

73. Inaba K, Teixeira PG, David JS, Chan LS, Salim A, Brown C, et al. Beta-blockers in isolated blunt head injury. J Am Coll Surg. 2008;206:432–8.

74. Riordan WP Jr, Cotton BA, Norris PR, Waitman LR, Jenkins JM, Morris JA Jr. Beta-blocker exposure in patients with severe traumatic brain injury (TBI) and cardiac uncoupling. J Trauma. 2007;63:503–10.

75. Arbabi S, Campion EM, Hemmila MR, Barker M, Dimo M, Ahrns KS, et al. Beta-blocker use is associated with improved outcomes in adult trauma patients. J Trauma. 2007;62:56–61.

76. Cotton BA, Snodgrass KB, Fleming SB, Carpenter RO, Kemp CD, Arbogast PG, et al. Beta-blocker exposure is associated with improved survival after severe traumatic brain injury. J Trauma. 2007;62:26–33.

77. Martin M, Mullenix P, Rhee P, Belzberg H, Demetriades D, Salim A. Troponin increases in the critically injured patient: mechanical trauma or physiologic stress? J Trauma. 2005;59:1086–91.

78. Little JR, Latchaw JP Jr, Slugg RM, Stowe NT. Treatment of acute focal cerebral ischemia with propranolol. Stroke. 1982;13:302–7.

79. Standefer M, Little JR. Improved neurological outcome in experimental focal cerebral ischemia treated with propranolol. Neurosurgery. 1986;18:136–40.

80. Junker V, Becker A, Huhne R, Zembatov M, Ravati A, Culmsee C, et al. Stimulation of beta-adrenoceptors activates astrocytes. Eur J Pharmacol. 2002;446:25–36.

81. Goyagi T, Kimura T, Nishikawa T, Tobe Y, Masaki Y. Beta-adrenoceptor antagonist attenuates brain injury after transient focal ischemia in rats. Anesth Analg. 2006;103:658–63.

82. Goyagi T. Neuroprotection (in Japanese). J Jpn Clin Anesth. 2007;27:588–98.

83. Prass K, Meisel C, Hoflich C, Braun J, Halle E, Wolf T, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by post-stroke T helper cell type 1 like immunostimulation. J Exp Med. 2003;198:725–36.

84. Nessler J, Nessler B, Kitlinski M, Gackowski A, Piwowarska W, Stepniewski M. Concentration of BNP, endothelin 1, pro-inflammatory cytokines (TNF-alpha, IL-6) and exercise capacity in patients with heart failure treated with carvedilol. Kardiol Pol. 2008;66:144–51.

85. Sachs D, Cunha FQ, Poole S, Ferreira SH. Tumor necrosis factor-alpha, interleukin-1 beta and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. Pain. 2002;96:89–97.

86. Nishio R, Shioi T, Sasayama S, Matsumori A. Carvedilol increases the production of interleukin-12 and interferon-gamma and improves the survival of mice infected with the encephalomyocarditis virus. J Am Coll Cardiol. 2003;41:340–5.

87. Klehmet J, Harms H, Richter M, Prass K, Volk HD, Dirnagl U, et al. Stroke-induced immunodepression and post-stroke infections: lessons from the preventive antibacterial therapy in stroke trial. Neuroscience. 2008;13:1–13.

88. Woiciechowsky C, Asadullah K, Nestler D, Eberhardt B, Platzer C, Schoning B, et al. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury. Nat Med. 1998;4:808–13.

89. Katafuchi T, Take S, Hori T. Roles of sympathetic nervous system in the suppression of cytotoxicity of splenic natural killer cells in the rat. J Physiol. 1993;465:343–57.

90. Cheng X, Liao YH, Li B, Yang YL, Zhang JY, Lu BJ, et al. Effects of early treatment with metoprolol on myocardial inflammatory cytokine expression and heart function in rats with acute myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi. 2005;33:448–52.

91. Li B, Liao YH, Cheng X, Ge H, Guo H, Wang M. Effects of carvedilol on cardiac cytokines expression and remodeling in rat with acute myocardial infarction. Int J Cardiol. 2006;111:247–55.

92. Prabhu SD, Chandrasekar B, Murray DR, Freeman GL. Beta-adrenergic blockade in developing heart failure. Effects on myocardial inflammatory cytokines, nitric oxide, and remodeling. Circulation. 2000;101:2103–9.

93. Gullestad L, Ueland T, Brunsviq A, Kiekshus J, Simonsen S, Froland SS. Effect of metoprolol on cytokine levels in chronic heart failure—a substudy in the metoprolol controlled-release randomized intervention trial in heart failure (MERIT-HF). Am Heart J. 2001;141:418–21.

94. Loiek A, Pecivova J, Macickova T, Nosal R, Papezikova I, Ciz M. Effect of carvedilol on the production of reactive oxygen species by HL-60 cells. Neuro Endocrinol Lett. 2008;29:779–83.

95. Lang CH, Nystrom G, Frost RA. Beta-adrenergic blockade exacerbates sepsis-induced changes in tumor necrosis factor alpha and interleukin-6 in skeletal muscle and is associated with impaired translation initiation. J Trauma. 2008;64:477–86.

96. Schmitz D, Wilsenack K, Lendemanns S, Schedlowski M, Oberbeck R. Beta-adrenergic blockade during systemic inflammation: impact on cellular immune functions and survival in a murine model of sepsis. Resuscitation. 2007;72:286–94.

97. Jeschke MG, Norbury WB, Finnerty CC, Branski LK, Herndon DN. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. J Trauma. 2007;62:676–81.

98. Oberbeck R. Catecholamines: physiological immunomodulators during health and illness. Curr Med Chem. 2006;13:1970–89.

99. Benish M, Bartal I, Goldfarb Y, Levi B, Avraham R, Raz A, et al. Perioperative use of beta-blockers and COX-2 inhibitors may improve immune competence and reduce the risk of tumor metastasis. Ann Surg Oncol. 2008;15:2042–52.

100. McBride WT, Armstrong MA, McBridge SJ. Immunomodulation: an important concept in modern anaesthesia. Anaesthesia. 1996;51:465–73.

101. Nquyen LP, Omoluabi O, Parra S, Frieske JM, Clement C, Ammar-Aouchiche Z, et al. Chronic exposure to beta-blockers

attenuates inflammation and mucin content in a murine asthma model. Am J Respir Cell Mol Biol. 2008;38:256–62.

102. Brimioulle S, Vachiery JL, Brichant JF, Delcroix M, Lejeune P, Naeije R. Sympathetic modulation of hypoxic pulmonary vasoconstriction in intact dogs. Cardiovasc Res. 1997;34:384–92.

103. Shirai M, Shindo T, Ninomiya I. Beta-adrenergic mechanisms attenuate hypoxic pulmonary vasoconstriction during systemic hypoxia in cats. Am J Physiol. 1994;266:H1777–85.

104. Turner DAB, Shribman AJ, Smith G, Achola KJ. Effect of halothane on cardiovascular and plasma catecholamine responses to tracheal intubation. Br J Anaesth. 1986;58:1365–70.

105. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation; influence of duration of laryngoscopy with or without lidocaine. Anesthesiology. 1977;47:381–4.

106. Angelard B, Debry C, Planquart X, Dubos S, Dominici L, Gondret R. Difficult intubation. A prospective study. Ann Otolaryngol Chir Cervicofac. 1991;108:241–3.

107. Bucx MJL, Van Geel RTM, Scheck PAE, Stijnen T. Cardiovascular effects of forces applied during laryngoscopy. The importance of tracheal intubation. Anaesthesia. 1992;47:1029–33.

108. Vohra A, Kumar S, Charlton AJ, Olukoga AO, Boulton AJ, McLeod D. Effect of diabetes mellitus on the cardiovascular responses to induction of anesthesia and tracheal intubation. Br J Anaesth. 1993;71:258–61.

109. Low JM, Harvey JT, Prys-Roberts C, Olukoga AO, Boulton AJ, McLeod D. Studies of anesthesia in relation to hypertension. VII. Adrenergic responses to laryngoscopy. Br J Anaesth. 1986;58:471–7.

110. Roy WL, Edelist G, Gilbert B. Myocardial ischemia during noncardiac surgery procedures in patients with coronary artery disease. Anesthesiology. 1979;51:393–7.

111. Fox EJ, Sklar GS, Hill CH, Villanueva R, King BD. Complications related to the pressure responses to endotracheal intubation. Anesthesiology. 1977;47:524–5.

112. Figueredo E, Garcia-Fuentes EM. Assessment of the efficacy of esmolol on the hemodynamic changes induced by laryngoscopy and tracheal intubation. Acta Anaesthesiol Scand. 2001;45:1011–22.

113. Mio Y. New ultra-short-acting beta-blockers: landiolol and esmolol(in Japanese). Masui. 2006;55:841–8.

114. Onaka M, Yamamoto H. Effects of continuous infusion of landiolol on the hemodynamic response to tracheal intubation (in Japanese). Masui. 2006;55:174–8.

115. Kitamura A, Sakamoto A, Inoue T, Ogawa R. Efficacy of an ultrashort-acting beta-adrenergic blocker (ONO-1101) in attenuating cardiovascular responses to endotracheal intubation. Eur J Clin Pharmacol. 1997;51:467–71.

116. Hasuo H, Tomiyasu S, Hojo M, Fujigaki T, Fukusaki M, Sumikawa K. Effect of ONO-1101, a novel short-acting beta-blocker, on hemodynamic responses to isoflurane inhalation and tracheal intubation. J Anesth. 1998;12:115–8.

117. Yamazaki A, Kinoshita H, Shimogai M, Fujii K, Nakahata K, Hironaka Y, et al. Landiolol attenuates tachycardia in response to endotracheal intubation without affecting blood pressure. Can J Anaesth. 2005;52:254–7.

118. Oda Y, Nishikawa K, Hase I, Asada A. The short-acting beta-1 adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. Anesth Analg. 2005;100:733–7.

119. Sugiura S, Seki S, Hidaka K, Masuoka M, Tsuchida H. The hemodynamic effects of landiolol, an ultra-short acting beta-1 selective blocker, on endotracheal intubation in patients with and without hypertension. Anesth Analg. 2007;104:124–9.

120. Dyson A, Isaac PA, Pennant JH, Giesecke AH, Lipton JM. Esmolol attenuates cardiovascular responses to extubation. Anesth Analg. 1990;71:675–8.

121. Kurian SM, Evans R, Fernandes NO, Sherry KM. The effect of an infusion of esmolol on the incidence of myocardial ischemia during tracheal extubation following coronary artery surgery. Anaesthesia. 2001;56:1163–8.

122. Kovac AL, Massingale A. Comparison of nicardipine versus esmolol in attenuating the hemodynamic responses to anesthesia emergence and extubation. J Cardiothorac Vasc Anesth. 2007;21:45–50.

123. Grillo P, Bruder N, Auquier P, Pellissier D, Gouin F. Esmolol blunts the cerebral blood flow velocity increase during emergence from anesthesia in neurosurgical patients. Anesth Analg. 2003;96:1145–9.

124. Nonaka A, Suzuki S, Abe F. The effects of continuous infusion of landiolol on heart rate changes after neostigmine-atropine administration during recovery from general anesthesia (in Japanese). Masui. 2006;55:1459–62.

125. Nakagawa H, Nanba M, Okayama Y. Landiolol prevented myocardial ischemia in a patient with severe aortic stenosis undergoing total gastrectomy (in Japanese). Masui. 2007;56:582–5.

126. Shirasaka T, Iwasaki T, Hosokawa N, Komatsu M, Kasaba T, Takasaki M. Effects of landiolol on the cardiovascular response during tracheal extubation. J Anesth. 2008;22:322–5.

127. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis risk in communities study. N Engl J Med. 2000;342:905–12.

128. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension. JAMA. 2004;292:2227–36.

129. Day JL, Metcalfe J, Simpson CN. Adrenergic mechanisms in control of plasma lipid concentration. Br Med J. 1982;284:1145–8.

130. Kjeldsen SE, Syvertsen JO, Hedner T. Cardiac conduction with diltiazem and beta-blockade combined. A review and report on cases. Blood Press. 1996;5:260–3.

131. Brouwer RM, Follath F, Buhler FR. Review of the cardiovascular adversity of the calcium antagonist beta-blocker combination: implications for antihypertensive therapy. J Cardiovasc Pharmacol. 1985;7:S38–44.

132. Westphal K, Weinbrenner A, Giessmann T, Stuhr M, Franke G, Zschiesche M, et al. Oral bioavailability of digoxin is enhanced by talinolol: evidence for involvement of intestinal P-glycoprotein. Clin Pharmacol Ther. 2000;68(1):6–12.

133. Lilja M, Jounela AJ, Juustila H, Mattila MJ. Interaction of clonidine and beta-blockers. Acta Med Scand. 1980;207:173–6.

134. Garvey HL, Woodhouse BL. Reversal of clonidine-induced hypotension by beta-adrenoceptor blocking drugs. Eur J Pharmacol. 1980;65:55–62.

135. Haidar SH, Moreton JE, Liang Z, Hoke JF, Muir KT, Eddington ND. The pharmacokinetics and electroencephalogram response of remifentanil alone and in combination with esmolol in the rat. Pharm Res. 1997;14:1817–23.

136. Haidar SH, Moreton JE, Liang Z, Hoke JF, Muir KT, Eddington ND. Evaluating a possible pharmacokinetic interaction between remifentanil and esmolol in the rat. J Pharm Sci. 1997;86:1278–82.

137. Zhou W, Fontenot HJ, Wang SN, Kennedy RH. Propofol-induced alterations in myocardial beta-adrenoceptor binding and responsiveness. Anesth Analg. 1999;89:604–8.

138. Hanouz JL, Riou B, Massias L, Lecarpentier Y, Coriat P. Interaction of halothane with alpha- and beta-adrenoceptor stimulations in rat myocardium. Anesthesiology. 1997;86:147–59.

139. Gueugniaud PY, Hanouz JL, Martino JM, Lecarpentier Y, Coriat P, Riou B. Interaction of halogenated anesthetics with dobutamine in rat myocardium. Anesthesiology. 1999;90:1663–70.

140. Hanouz JL, Vivien B, Gueugniaud PY, Lecarpentier Y, Coriat P, Riou B. Interaction of isoflurane and sevoflurane with alpha- and beta-adrenoceptor stimulations in rat myocardium. Anesthesiology. 1998;88:1249–58.