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Pharmacological modification of the perioperative stress response in noncardiac surgery

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The perioperative period is associated with alterations in the neuroendocrine, metabolic, and immune systems, referred to as "stress response." The resultant increased sympathetic activity and elevated serum concentrations of catecholamines may adversely affect the cardiovascular system, resulting in cardiovascular instability (hypertension, tachycardia, and arrhythmia), morbidity (myocardial ischemia, myocardial infarction, and stroke), and mortality (cardiac death and fatal stroke), particularly in patients at an elevated cardiovascular risk and with reduced cardiovascular reserve. Various strategies have been used to ameliorate the adverse perioperative cardiovascular sequelae of the perioperative stress response. Effective pharmacologic blunting of the stress response plays a crucial role in perioperative cardiac risk reduction strategies. In this context, the role of beta-adrenoceptor blockers, alpha$_2$-adrenoceptor agonists, and statins has been extensively examined. This chapter evaluates the available evidence with respect to treatment efficacy of these commonly prescribed drugs in patients undergoing noncardiac surgery.

Introduction

The perioperative period is associated with alterations in the neuroendocrine, metabolic, and immune system, referred to as "stress response." [1] It is triggered by activation of the

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hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. Hypothalamic activation of the sympathetic nervous system increases secretion of catecholamines from the adrenal medulla and releases norepinephrine from the presynaptic nerve terminals. Activation of the hypothalamus–pituitary–adrenal axis persists for at least 1 week following surgery. The increased sympathetic activity and elevated serum concentrations of catecholamines may adversely affect the cardiovascular system resulting in cardiovascular instability (hypertension, tachycardia, and arrhythmia), morbidity (myocardial ischemia, myocardial infarction, and stroke) and mortality (cardiac death and fatal stroke), particularly in patients at an elevated cardiovascular risk and with reduced cardiovascular reserve.

Various strategies have been employed to ameliorate the adverse perioperative cardiovascular sequelae of the perioperative stress response [2,3]. Considering the pathophysiology of coronary artery disease [4,5], the cardioprotective efficacy of the optimal medical therapy in patients with clinically relevant coronary artery disease [6], the questionable additional benefit of coronary revascularization in secondary cardiac prevention [7], the morbidity and mortality associated with coronary artery revascularization in high-risk patients [8], the lack of proven benefit of a prophylactic preoperative coronary revascularization [9,10], the etiology of perioperative myocardial infarction [11,12], and the increased perioperative risk of patients with coronary artery stents [13,14], effective pharmacologic blunting of the stress response plays a crucial role in perioperative cardiac risk reduction strategies. In this context, the role of beta-adrenoceptor blockers (BBs), alpha$_2$ (α_2)-adrenoceptor agonists, and statins has been extensively examined. This chapter evaluates the available evidence with respect to treatment efficacy of these commonly prescribed drugs in patients undergoing noncardiac surgery.

Beta blockers

Mechanisms of action

Perioperative adrenal cortical stimulation is accompanied by sympathetic nervous system-induced adrenal medullary activation, resulting in the release of catecholamines with subsequent stimulation of cardiovascular adrenergic receptors. This increases each of the four determinants of myocardial oxygen (O_2) consumption (heart rate, preload, afterload, and contractility). In addition, beta-adrenoceptors mediate myocyte apoptosis and direct myocyte toxicity.

Numerous cardiovascular and other effects of BBs may exert perioperative cardioprotection [15,16]. BBs decrease sympathetic tone and myocardial contractility. The resultant decreases in heart rate and arterial pressure and the prolongation of diastolic filling time reduce myocardial O_2 consumption and increase myocardial O_2 supply, thereby improving the myocardial O_2 supply/demand balance. BBs may further reduce myocardial O_2 consumption by blunting hemodynamic stress responses and by inhibiting lipolysis, which causes the myocardium to metabolize more glucose in relation to free fatty acids [15]. In addition, they decrease beta$_2$-adrenoceptor-mediated release of intracardiac norepinephrine during ischemia (reducing cardiac toxicity), attenuate exercise-induced coronary vasoconstriction (improving exercise capacity), have anti-arrhythmic properties (increasing the threshold for ventricular fibrillation during myocardial ischemia), alter gene expression and receptor activity [17,18], and protect against apoptosis. Their anti-inflammatory effects [19,20] may contribute to stabilization of the atherosclerotic plaques [21]. Beta blockers may further contribute to coronary artery plaque stabilization by reducing coronary artery shear stress as a consequence of reduced coronary blood flow velocity following reduction in myocardial contractility.

Randomized controlled trials

Two randomized controlled trials (RCTs) in the 1990s by Mangano et al. [22] and Poldermans et al. [23] provided seemingly strong support for the efficacy of perioperative beta blockade in reducing morbidity and mortality after noncardiac surgery. Primarily based on these studies, routine preoperative initiation of BBs in patients at medium or high risk for perioperative adverse cardiovascular events undergoing noncardiac surgery was advocated by practice guidelines and considered the standard of care worldwide [24]. However, both studies had serious methodological limitations that preclude any valid conclusions [25]. Several subsequent publications from the Poldermans group