

Sympatho-modulatory therapies in perioperative medicine

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With increasing life expectancy and improved surgical technology an ever-larger number of elderly patients with cardiovascular disease, or significant cardiovascular risk factors will undergo major surgery. More than 5% of an unselected surgical population undergoing non-cardiac surgery will suffer from perioperative cardiovascular complications including myocardial infarction and cardiac death. The incidence of adverse cardiac events may even reach 30% in high-risk patients undergoing vascular surgery causing a substantial financial burden of perioperative health care costs.⁵⁹ Thus, all therapeutic measures should be undertaken to reach the challenging goal of a lower incidence of perioperative cardiovascular complications.

Gaining control over sympathetic nervous system activity, that is blunting the adrenergic response to the surgical trauma, traditionally represents an important aspect of anaesthetic practice.²¹ Anaesthesiology has been regarded as the 'practice of autonomic nervous system medicine'. While variable and moderate changes in sympathetic nervous system activity function as a servo-control mechanism and are even required to maintain and optimize cardiac performance, undue liberation of excitotoxic substances such as catecholamines and inflammatory cytokines, particularly during emergence from anaesthesia and the painful postoperative period, facilitates the occurrence of cardiovascular complications.^{83 84} At this point, the life-supporting adrenergic drive ('fight-or-flight-response') turns into a potentially hazardous life-threatening maladaptation. In support of this concept, the beneficial effects of anti-adrenergic treatment regimens in perioperative medicine have been confirmed, in observational studies, meta-analyses^{5 51 66} and randomized controlled clinical trials.^{43 54 59 63 80 84} However, the seemingly established concept of 'sympatholysis' as an effective cardioprotective

treatment modality needs considerable refinement in the light of the many new experimental and clinical findings. The parlance of 'sympatholytic' protection erroneously equates annihilation of any type of adrenergic stimulation with cardioprotection and should be replaced by 'sympatho-modulatory' protection.

The present review summarizes findings from large-scale heart failure trials and discusses basic and clinical aspects of individual sympatho-modulatory therapies, as currently used in perioperative medicine, including β -adrenergic antagonism, α_2 -agonism, and regional anaesthetic techniques. For limitation of space, reviews will often be cited where further references to the primary literature may be found.

Adrenergic activity in the heart: a double-edged sword

Changing therapeutic paradigms: a historical perspective

Over several decades, the basic ideas on the role of the sympathetic nervous system in healthy and diseased myocardium have required repeated re-evaluation. In 1960, Braunwald and colleagues at the National Institutes of Health reported for the first time on adrenergic dysfunction in the failing heart. Based on reduced noradrenaline levels in failing myocardial tissue and the adverse short-term effects of high doses of anti-adrenergic agents,²⁵ it became widely accepted that sufficient and—in the case of heart failure—supportive adrenergic drive would be needed to ensure normal cardiac function. Fifteen years later in the late 1970s, this therapeutic concept was challenged by the following findings summarized in

reference¹³. First, chronically administered β -adrenergic antagonists (β -AAs) exhibited beneficial effects in idiopathic dilated cardiomyopathies. Secondly, β -adrenergic receptor (β -AR) down-regulation was detected in failing myocardium as a consequence of excessive adrenergic drive. Thirdly, despite decreased noradrenaline stores in failing myocardial tissue, coronary sinus blood exhibited increased noradrenaline release. These findings led to a new 'counterintuitive' therapeutic strategy whereby anti-adrenergic treatment was considered beneficial in the failing heart. This concept has dominated therapeutic thinking in cardiology for almost 20 years. However, most recent results from basic science and clinical studies again questioned this 'dogma' and called for further refinement of the concept.¹² First, moxonidine, a centrally active imidazoline agonist, which lowers noradrenaline spill-over in myocardial tissue and even reverses catecholamine-induced remodelling in the myocardium, increased mortality by more than 50% in the Moxonidine Congestive Heart Failure Trial (MOXCON).¹⁷ This is in accordance with experimental results from a canine heart failure model where dopamine β -hydroxylase inhibition resulting in decreased noradrenaline levels did not improve left ventricular function.⁶⁹ Secondly, in the β -Blocker Evaluation of Survival Trial (BEST), bucindolol increased mortality disproportionately in black NYHA Class IV patients, although the overall benefit of bucindolol still prevailed in the whole bucindolol cohort when compared with placebo.⁶ It was speculated that pronounced β_2 -AR antagonism, which excessively decreases pre-synaptic noradrenaline release, in conjunction with unopposed α_1 -block could be responsible for the observed adverse effects. Collectively, these findings seriously challenged the overly simple dogma of 'sympatholytic equals beneficial'. Irreversible removal of adrenergic support with the inability to recruit compensatory adrenergic drive when required to maintain adequate cardiac function is obviously detrimental. Moreover, these observations highlight the fundamentally differential biological consequences between 'unselective inhibition of adrenergic drive', which may be achieved by central inhibition of the sympathetic tone vs selective peripheral receptor-targeted block.

Implications for perioperative medicine

Hyperadrenergic drive is a hallmark of the perioperative stress response. Maladaptive alterations in the autonomic nervous system, such as down-regulation of adrenergic receptors and autonomic imbalance, persist for weeks after surgery.¹ Activation of the sympathetic nervous system, particularly β -ARs dramatically increases heart rate and oxygen consumption, and plays a central role in the development of perioperative ischaemia. Patients with coronary artery disease, risk factors for coronary artery disease or specific genetic polymorphisms may be particularly sensitive to catecholamine toxicity and prone to

perioperative ischaemia and cardiac complications. Current knowledge suggests significant protection from maladaptive adrenergic activity by selective inhibition and/or activation of specific β/α -AR subtypes.⁸³ Identification of patients with critical genetic polymorphisms associated with adverse outcome as part of perioperative risk assessment may directly improve patient management by adequate timely pharmacological interventions and decrease perioperative mortality. Unfortunately, at present the pharmacological armamentarium is still limited with respect to receptor-subtype selectivity. Pan-adrenergic inhibition of the sympathetic nervous system may not represent the optimal cardioprotective treatment modality in perioperative medicine. Irreversible removal of adrenergic support with the inability to maintain adequate cardiac function may be detrimental.

Sympatho-modulation by medication

Alpha2-agonists and the cardiovascular system

Basic mechanisms and cardiovascular effects

α_2 -Agonists exert their cardioprotective effects predominantly by attenuation of catecholamine release and thus inhibition of stress-induced tachycardia. The hypotensive effect of this class of drugs is achieved by lowering central sympathetic tone via activation of α_{2A} -ARs and the pharmacologically less well-defined imidazoline1 receptors. This is consistent with the notion that clonidine is ineffective in controlling increased arterial pressure in hypertensive tetraplegic patients.⁴⁴ In contrast, bradycardic effects are elicited by vagomimetic effects, and are preserved in tetraplegic patients.⁶⁴ Apart from their haemodynamic effects, α_2 -agonists may induce analgesia (particularly for sympathetically maintained pain), anxiolysis, and sedation.^{32 34} Post-junctional α_{2B} -ARs mediate the short-term hypertensive response seen with these drugs via stimulation of L-type Ca^{2+} channels in smooth muscle cells of resistance vessels. Recently, etomidate was found to activate α_{2B} -ARs thereby eliciting its well-known stabilizing cardiovascular effect.⁵⁵ Pre-junctional α_{2A} -ARs have anti-adrenergic effects, and post-junctional α_{2A} -ARs have anaesthetic effects via inhibition of L-type Ca^{2+} channels in neurons localized in the locus coeruleus and nucleus reticularis lateralis. Decreased ganglionic transmission and a concomitant increase of the counterregulatory vagal tone can further enhance the central effects of α_2 -agonist.⁴⁵ Interestingly, the anti-arrhythmic effects of α_2 -agonists are completely mediated via the vagal nerve, as anti-arrhythmic effects are totally abolished by vagotomy.³⁰ One of the potential advantages of central inhibition of sympathetic tone over peripheral receptor block is that the release of co-transmitters such as neuropeptide-Y, a major contributor to coronary vascular resistance, is equally suppressed. On the other hand, these neurotransmitters may exert trophic effects on cardiomyocytes. All α_2 -agonists interact with

Table 1 α_2 -Agonists and specific properties. +=effect present; I1*=centrally located imidazoline receptor-1; /=not known

Drug	Selectivity ratio of α_2/α_1	Selectivity ratio of $\alpha_2/I1^*$	Plasma half-life	Lipid solubility	Clearance	Special
Clonidine	40	16	9 h	+	Hepatic/renal	Sedative Analgesic Anti-shivering Anti-sialagogue Neuromuscular blocking agents
Mivazerol	400	215	4 h	+	Hepatic/renal	
Dexmedetomidine	1600	30	2 h	+	Hepatic/renal	
Moxonidine	/	70	2 h	+	Hepatic/renal	

imidazoline receptors because of their imidazole ring. Although the novel α_2 -agonist moxonidine was developed to preferentially interact with imidazoline binding sites, it requires the α_2 -AR to lower arterial pressure as no hypotensive effects in response to moxonidine were observed in α_2 -AR knockout mice.⁷⁸ As with β -ARs, α -ARs can be up- or down-regulated.⁷⁴ However, their regulation and the subsequent physiological consequences are poorly understood. Unfortunately, there are no subtype-selective agonists clinically available. At present, the most commonly used α_2 -agonists are clonidine and dexmedetomidine. Their relative receptor specificities as compared with other α_2 -agonists are listed in Table 1.

Clinical aspects and considerations

A recent meta-analysis on the efficacy of clonidine for the prevention of perioperative myocardial ischaemia included seven studies and concluded that clonidine reduces cardiac ischaemic events in patients who either have or are at risk of coronary artery disease, without increasing the incidence of bradycardia.⁵¹ Interestingly, this meta-analysis found a reduction in myocardial ischaemia by clonidine in cardiac and non-cardiac surgery, but only in the oral (mostly preoperative), but not the i.v. administration group. Mortality associated with myocardial ischaemia was not evaluated in this meta-analysis because of the expected low number of myocardial infarctions and cardiac deaths. Another recent meta-analysis included studies with all α_2 -agonists claimed a lower cardiac morbidity in high-risk patients undergoing vascular and major surgery.⁸² Clonidine has also been found to decrease anaesthetic-induced impairment of the baroreflex responses and thus to attenuate arterial pressure lability (smaller haemodynamic fluctuations around a lower basal arterial pressure).⁵⁷ Similarly, perioperative mivazerol has been reported to decrease the occurrence of perioperative ischaemic events, and recently to decrease cardiac death (9.5 vs 14% in placebo, $P=0.02$), but not myocardial infarction, in patients with coronary artery disease undergoing vascular surgery.⁵⁴ However, there was no effect of mivazerol on the incidence of all-cause deaths, cardiac deaths, or myocardial infarctions in the whole cohort of study patients (undergoing all types of surgery). There is currently less evidence for α_2 -agonists than β -AA to decrease perioperative cardiovascular mortality. However, apart from their cardiovascular effects, α_2 -agonists may exert indirect beneficial

cardiac effects by their non-ceiling analgesic, anti-shivering, and sedative effects. Sudden discontinuation should be avoided because of the risk of withdrawal syndrome.⁸³ Theoretically, α_2 -agonists can jeopardize coronary flow reserve, as intracoronary application of α_2 -antagonist yohimbine was shown to attenuate inhibition of coronary flow in patients undergoing coronary culprit lesion stenting.²⁷ Conversely, α -adrenergic vasoconstriction reduces systolic retrograde coronary blood flow maintaining sufficient perfusion in subendocardial myocardium during adrenergic stimulation.⁴⁸ Bradycardia as a side-effect should be primarily treated with atropine, but higher doses of clonidine can markedly blunt the effect of atropine.⁴⁹ Conversely, clonidine may significantly potentiate the pressor effects of catecholamines.⁵⁰ At higher concentrations, α_2 -agonists may promote coagulation.⁷⁹ Although detrimental cardiac effects were reported after long-term use of α_2 -agonists in heart failure patients, the short-term use of α_2 -agonists at moderate doses (thrombotic complications are possible with high doses) in perioperative medicine can be advocated. Nonetheless, more selective modulation of α_2 -ARs would be highly desirable.

β -AAs and the cardiovascular system

Basic mechanisms and cardiovascular effects

Although some effects of β -AAs may be caused by central actions,⁷²⁻⁸⁵ β -AAs in principle mediate their effects directly at the end-organ receptor level by decreasing β -AR signalling. This is fundamentally different from most of the α_2 -agonist-mediated effects. Important mechanisms responsible for β -AA-mediated perioperative cardioprotection are:⁸³

- Blunting of stress-induced increases in heart rate optimizing myocardial oxygen balance and stabilizing atherosclerotic plaques.
- Improved Ca^{2+} handling and bioenergetics shifting ATP production from oxidation of free fatty acid to less oxygen consuming glucose oxidation.
- Prevention of target protein hyperphosphorylation leading to decreased receptor desensitization and diastolic Ca^{2+} leakage by the ryanodine receptor.
- Inhibition of β_1 -AR-mediated cytotoxicity (altered gene expression, mechanical unloading, apoptosis, necrosis).
- Anti-arrhythmic effects.

Table 2 β -AAs and ancillary properties. NO, nitric oxide; +=effect present; -=effect absent; ?=still under debate

Drug	Selectivity ratio of β_1/β_2	Membrane stabilizing activity	Intrinsic sympathomimetic activity	Lipid solubility	Clearance	Special
Propranolol	2.1	+	–	+++	Hepatic	Inverse agonist
Metoprolol	74	–	–	+	Hepatic stereoselective	Inverse agonist-AR
Atenolol	75	–	–	–	Renal	–
Esmolol	70	–	–	–	Erythrocyte esterase	–
Bisoprolol	119	–	–	(+)	Hepatic/renal	–
Celiprolol	~300	–	β_2+	–	Hepatic/renal	β_2 -agonist
Nebivolol	293	–	–	+	Hepatic	NO-release bronchodilation
Carvedilol	7.2	–	β_1 +(?)	+	Hepatic, stereo-selective	Anti-oxidant, anti-adhesive. α_1 -antagonist, β -AR↓
Bucindolol	1.4	–	+(?)	+	Hepatic	α_1 -antagonist

In contrast to α_2 -agonists, untoward peripheral effects of β -AAs can be offset by counter-regulatory production of endogenous catecholamines explaining the good tolerability of this class of drugs.^{26 43 59 84} On the other hand, direct receptor block may be more cytoprotective under supra-maximal autonomic stimulation (flat part of the sigmoid dose–response curve) than simply lowering catecholamine levels as observed with α_2 -agonist treatment. Finally, selective inhibition of the β_1 -AR-mediated toxic effects leaves the beneficial effects of moderate β_2 -AR-stimulation unaffected and thus may further improve haemodynamic tolerance.⁸³ Notably, β_1 -AR antagonism enhances inotropic response to β_2 -AR stimulation.²⁹ β_1 -AR-block may increase post-ischaemic and pharmacologic coronary flow velocity reserve.⁷ Although many ancillary properties of individual β -AAs are thought to be linked to clinical effectiveness and tolerability,⁷⁵ their significance in perioperative medicine needs to be elucidated. The selection of a specific agent over another on the basis of individual drug profiles may be advantageous in specific clinical situations (Table 2). As with clonidine, β -AAs improve the baroreflex sensitivity in elderly hypertensive patients, thus stabilizing arterial pressure.¹⁶

Clinical aspects and considerations

The evidence for the effectiveness of β -AAs in reducing perioperative cardiac events has been extensively reviewed.^{2 62} Based on the clinical evidence of mainly two well-designed randomized clinical trials,^{43 59} the perioperative use of β -AAs has been firmly supported in the updated (2002) guidelines on perioperative evaluation of patients undergoing non-cardiac surgery of the American Heart Association (AHA).²⁰ Mangano and colleagues showed in a cohort of elderly male patients with coronary artery disease or at risk of coronary artery disease undergoing major surgery (predominantly abdominal and vascular) that perioperative atenolol administration decreased long-term overall mortality by 55% and cardiac mortality by 65%.⁴³ Comparing bisoprolol with standard care, Poldermans and colleagues demonstrated a 10-fold reduction in the 30-day perioperative incidence of cardiac death and non-fatal

myocardial infarction in patients with positive dobutamine stress echocardiography undergoing vascular surgery.⁵⁹ Although these randomized clinical studies have been extensively criticized on a number of grounds,^{42 62} β -AA treatment represents undoubtedly the most effective treatment modality to prevent perioperative cardiac complications. According to the AHA guidelines, all patients with chronic β -AA treatment, or definite coronary artery disease undergoing major vascular surgery should be treated with perioperative β -AAs (Class I evidence for β -AAs). All other indications for the preventive use of perioperative β -AAs are less well supported by current evidence and need further clarification in randomized clinical studies.³⁶ In a recent editorial accompanying an article by London and colleagues⁴² on the physiologic foundations and clinical controversies of perioperative β -AA treatment, Kertai and colleagues³³ recommended the widespread use of perioperative β -AA treatment in all surgical patients with only a single risk factor as well as the long-term continuation of such a treatment after surgery. We would like to stress, however, that such type of high-impact recommendations should be based on more solid facts, namely randomized controlled trials. In no case should these suggestions hinder necessary future research in this important area and render the conduct of randomized controlled trials evaluating perioperative β -AA treatment impossible because of unjustified ethical objections and/or misperceptions about the currently available evidence.

Patients with chronic β -AA treatment may need substantial perioperative supplementation. The currently recommended use of atenolol, bisoprolol, and metoprolol is remarkably cheap and safe if cautiously titrated.⁷⁰ Whenever bradycardia occurs, it is important to decide whether discontinuation of treatment is really necessary. Although titration of β -AAs to individual ischaemic thresholds using non-invasive stress tests appears rational, particularly with respect to side-effects,⁶³ it is hardly applicable in the clinical setting (too expensive, many patients with pre-existing ST-segment changes or left-bundle branch block). Also, the artificial conditions during non-invasive stress tests cannot entirely simulate the real

perioperative conditions with significant changes in coagulation and cytokine release. β -AAs should be initiated as early as possible (ideally weeks before surgery), maintained for at least 1 week up to 1 month (in vascular patients), and tapered before discontinuation to avoid adrenergic withdrawal response. In no case should administration of β -AAs serve to circumvent important preoperative risk stratification or possible invasive interventions.²³ Responses of α - and β -AR may be altered by down-regulation and desensitization in sepsis, burns, cirrhosis, haemorrhagic shock, and cardiopulmonary bypass.⁷⁴ Polymorphic metabolism of β -AA may significantly affect clinical responsiveness. Accordingly, poor metabolizers with different variants of CYP2D6 (cytochrome P450 isoform) may have increased plasma levels of metoprolol.³¹ This is not the case for bisoprolol, which is independent of any genetic polymorphism of oxidation.³⁸ Genetic background also appears to be responsible for observed variability in efficiency of β -AA treatment in black and Asian patients.⁶ Finally, β -AAs are of questionable value in heart failure patients with atrial fibrillation.²⁴ Thus, one can speculate that their perioperative administration in cardiac risk patients with atrial fibrillation might be of minimal or no advantage. Importantly, coronary artery disease represents a severe inflammatory process affecting the whole coronary tree ('pancoronary'). As the localization of perioperative myocardial infarction is related only in 50% to the culprit coronary lesion or the site of the most critical coronary stenoses,¹⁸ preoperative invasive interventions such as angioplasty or coronary surgery may not replace but rather complete the protection afforded by perioperative β -AA treatment. Whether the protection by perioperative β -AA treatment can be enhanced by additional administration of statins, must be evaluated in future randomized controlled trials. Perioperative β -AA treatment should be used in accordance with available data obtained from perioperative randomized controlled trials. Recent findings from perioperative randomized clinical trials offer a strong foundation for β -AA-mediated cardioprotection.

Sympatho-modulation by regional anaesthesia/analgesia

General comments

Approximately one-third of patients undergo regional anaesthesia for surgery. The anaesthetic and analgesic power of epidural anaesthesia has been recently reinforced by reports on coronary artery bypass grafting in awake patients under epidural anaesthesia.³ In general, regional anaesthesia more effectively decreases the neurohumoral response to surgery than general anaesthesia, particularly with respect to the release of adrenal cortical and medullary hormones. Although some meta-analyses claim regional anaesthesia/analgesia to be superior to general anaesthesia

with respect to cardiovascular and other outcome measures (deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia and other infections, respiratory failure, renal failure, stroke),^{4,5,66} most large-scale randomized trials clearly demonstrated that the choice of anaesthesia does not influence cardiac morbidity and mortality.^{52,56,58,65} Hence, based on the currently available clinical data, the opinion prevails that factors other than type of anaesthesia are more important for cardiac outcome in even high-risk patients. However, uncertainty about the ultimate net benefits of regional anaesthesia compared with general anaesthesia remains.

Spinal anaesthesia

Basic mechanisms and cardiovascular effects in spinal anaesthesia

Block of sympathetic nerves (T1-L2, cardiac accelerator nerves T1-T5) can lead to sudden profound physiological changes during spinal anaesthesia. A rapid distribution of the local anaesthetic in the subarachnoid space results in the block of all fibres of the anterior and posterior spinal roots including the sympathetic afferent and efferent fibres. Spinal cord penetration of the local anaesthetic may be also responsible for specific anaesthetic effects. The short diffusion path to small diameter B- and C-fibres makes them specifically susceptible to local anaesthetic action. Much more than in epidural anaesthesia/analgesia, the degree of sympathetic denervation is often unpredictable and quite extensive, albeit for a relatively limited time. Importantly, the level of sympathetic block exceeds that of the sensory block usually by two dermatomes, but may be more than six dermatomes.¹⁵ The level of the block depends on age and position of the patient. Levels above T1 not only decrease venous return and thereby slow heart rate, but also abolish completely the sympathetic cardiac drive. Hypotension in spinal anaesthesia is predominantly a result of the marked decrease in venous return followed by a decrease in cardiac output (reduced by 20%) and stroke volume (reduced by 25%). Systemic vascular resistance nearly remains unaffected (–5%), that is there is minimal arteriolar dilation. In contrast to general anaesthesia, no down-regulation of lymphocyte β -ARs was observed after Caesarean section when performed under spinal anaesthesia. The beneficial effects on β -AR-preservation, stress response, and haemodynamics were also recently shown in patients undergoing coronary artery bypass grafting with a high spinal anaesthesia as an adjunct to general anaesthesia.³⁷

Clinical aspects and considerations in spinal anaesthesia

The incidence of cardiac arrest in spinal anaesthesia is significant (estimated at 1:10 000) and is thought to be mainly a result of sympatho-vagal dysbalance.¹⁴ Risk factors for cardiac arrest under spinal (and epidural) anaesthesia are: male gender, heart rate less than 60 beats

min⁻¹, ASA Physical Status-I (i.e. healthy individuals), β -AA use, age less than 50 yr, and sensory levels above T6.^{14,60} Marked hypotension may occur in 30% and bradycardia in 15% of patients. Pre-hydration, slow injection of the local anaesthetic, and unilateral block may help to decrease adverse haemodynamic effects.⁴⁰ Incremental continuous spinal anaesthesia may provoke significantly less hypotensive episodes and ischaemic cardiac events than bolus injection.²² Cardiovascular side-effects may occur at any time during spinal anaesthesia and even develop hours after surgery.⁶¹ Overall, the sympathetic denervation achieved by spinal anaesthesia is fairly unpredictable, rather transient (except for continuous spinal anaesthesia), and associated with a remarkably high incidence of haemodynamic instability and cardiac arrest.

Epidural anaesthesia/analgesia

Basic mechanisms and cardiovascular effects

The dorsal and ventral roots are the primary sites of action in epidural anaesthesia. However, local anaesthetics can also cross the dura and penetrate the spinal cord. In general, sensory anaesthesia is established before a sympathetic block sufficient to induce systemic hypotension. Changes in arterial pressure, heart rate, and cardiac output reflect the level of the block, but are in general less pronounced than in spinal anaesthesia. Below T5, there is rarely hypotension as compensatory vasoconstriction in unblocked segments occurs. In other words, the vasodilation below the level of sympathetic block is usually compensated for by vasoconstriction above the level of block, such that the decrease in arterial pressure is relatively mild. Above T5, cardiac fibres may be affected and no compensatory vasoconstriction may occur leading to marked hypotension, particularly in hypovolaemic patients.¹¹ Levels up to T10 increase the lower limb blood flow, but do not change coronary blood flow, provided there is no decrease in arterial pressure.⁷³ High levels (>T5) cause a decrease in coronary blood flow by up to 50% and an increase in coronary vascular resistance. However, as myocardial work is concomitantly decreased to a greater degree (decreased heart rate and contractility), no adverse effects may be seen. Hypotension in lumbar epidural anaesthesia may have opposite effects on cardiac oxygen balance. Compensatory reflex activity in unblocked thoracic sympathetic segments may decrease coronary blood supply and provoke wall motion abnormalities.⁶⁸ Hypotension in lumbar epidural anaesthesia (T6-T12) may be therefore more critical in susceptible patients. However, lumbar and thoracic epidural anaesthesia have both been reported to decrease left ventricular loading and improve global and regional ventricular function in patients with coronary artery disease. Thoracic epidural anaesthesia additionally increases the diameter of stenotic coronary arteries.⁹ As with β -AA treatment, there is a redistribution from the epicardial to the endocardial blood flow in thoracic epidural anaesthesia.³⁵ The use of thoracic epidural

anaesthesia decreases ST-segment changes and infarct size after coronary artery occlusion and may improve post-ischaemic functional recovery (less stunning).⁴⁷

Clinical aspects and considerations in epidural anaesthesia/analgesia

Thoracic epidural anaesthesia was reported to be effective in humans with myocardial ischaemia refractory to conventional medical treatment indicating that under specific conditions thoracic epidural anaesthesia may be superior to anti-anginal medication.³ Although some studies claim that the use of epidural anaesthesia with or without general anaesthesia would improve perioperative cardiac outcome, there is currently little evidence from large-scale randomized controlled trials to support this view. Disappointingly, a large multicentre, randomized, unblinded study with 973 patients was unable to detect decreased 30-day mortality in patients undergoing abdominal surgery with epidural (thoracic or lumbar)/general anaesthesia plus postoperative epidural analgesia vs general anaesthesia alone.⁵⁶ These findings reiterate the observations made by other investigators.^{53,81} However, postoperative epidural analgesia was found to significantly improve pulmonary outcome in a recent meta-analysis.⁴ Pulmonary dysfunction, stroke, acute renal failure, and acute confusion were also less frequently observed in patients undergoing coronary artery bypass graft surgery when receiving postoperative thoracic epidural analgesia.⁷¹ By inhibition of sympathetic spinal reflexes, thoracic epidural anaesthesia, in contrast to clonidine or dexmedetomidine, can prevent bowel dysfunction after abdominal surgery and improve gastrointestinal recovery. Notably, high thoracic epidural anaesthesia can be used safely in patients with bronchial hyper-reactivity.²⁸ Although not directly compared with respect to cardioprotection, lumbar epidural anaesthesia does not appear to offer the same degree of protection. Serious complications including post-dural puncture headache, neurologic injury, and epidural haematoma (<1:100 000) with paraplegia may be lower at the thoracic level. Collectively, thoracic epidural anaesthesia is a unique treatment modality combining effective pain relief with anti-adrenergic properties. It also has the theoretical advantage of a lower cardiac complication rate in high-risk patients undergoing major surgery.⁴¹

Sympatho-modulatory therapies: does it make sense to combine them?

Different anti-adrenergic therapies affect the autonomic nervous system activity by different mechanisms and accordingly differentially modulate haemodynamics (Table 3). Thus, the question arises of whether these treatment modalities should be combined to optimize cardiac protection. Some combinations such as β -AAs or α_2 -agonists with regional anaesthesia are occasionally used, but have not been prospectively evaluated with respect to

Table 3 Differential haemodynamic effects of individual, acutely established sympatho-modulatory therapies. β -AA, β -adrenergic antagonist; α_2 -A, α_2 -agonist; BP, arterial pressure; CO, cardiac output; CVR, coronary vascular resistance; HR, heart rate; LEA, lumbar epidural anaesthesia; LVEDP, left ventricular end-diastolic pressure; SA, spinal anaesthesia; SVR, systemic vascular resistance; TEA, thoracic epidural anaesthesia; VO_2 myocardium, myocardial oxygen consumption; \downarrow =decreased; \uparrow =increased; \leftrightarrow =unchanged; ()=variable

Parameter	Treatment				
	β -AA	α_2 -A	LEA	TEA	SA
HR	\downarrow	\downarrow	$\downarrow/\leftrightarrow$	\downarrow	\downarrow
BP	\downarrow	$(\uparrow)/\downarrow$	\downarrow	\downarrow	\downarrow
SVR	(\uparrow)	\downarrow	\downarrow	(\leftrightarrow)	(\leftrightarrow)
Afterload	\downarrow	\downarrow	\downarrow	(\leftrightarrow)	(\leftrightarrow)
LVEDP	\uparrow	\uparrow	\downarrow	\downarrow	\downarrow
CO	\downarrow	\downarrow	\downarrow	\downarrow	\downarrow
CVR	\leftrightarrow	\leftrightarrow	$\leftrightarrow/(\uparrow)$	(\downarrow)	$\leftrightarrow/(\uparrow)$
VO_2 myocardium	\downarrow	\downarrow	(\uparrow)	\downarrow	(\downarrow)
Arrhythmia	\downarrow	(\downarrow)	\leftrightarrow	\downarrow	\leftrightarrow

cardiac outcome and adverse effects. There is sparse clinical and experimental data on efficacy and side-effects of combined anti-adrenergic treatments. A comparison between thoracic epidural anaesthesia and β -AA on haemodynamic parameters in conscious rats with acute myocardial infarction revealed the following intriguing findings.¹⁰ While thoracic epidural anaesthesia decreased left ventricular end-diastolic pressure and systemic vascular resistance remained unaffected, metoprolol in contrast increased both parameters. Heart rate and cardiac output were similarly decreased in both treatment regimens. Importantly, induction of thoracic epidural anaesthesia during maximal metoprolol treatment did not cause any further haemodynamic changes (particularly no further decline in arterial pressure). Similarly, in a clinical study evaluating the effect of thoracic epidural anaesthesia (T1-T12) on cardiovascular function in patients with coronary artery disease receiving β -AAs, no further cardiac depression (decrease in arterial pressure and heart rate) occurred.⁷⁶ From this, it can be speculated that the favourable haemodynamic effects of thoracic epidural anaesthesia may be synergistic with the documented life-saving effects of β -AAs. Good haemodynamic tolerance of β -AAs combined with epidural anaesthesia has been reported perioperatively in some clinical studies with small numbers of patients.^{59,80} Intrathecal and oral clonidine prolongs regional anaesthesia/analgesia but increases the incidence of hypotension and bradycardia.¹⁹ Importantly, correction of epidural anaesthesia-induced hypotension may provoke transient myocardial ischaemia.⁶⁷ Although the incidence of bradycardia and hypotension may be significantly increased with the combination of regional anaesthetic techniques and β -AAs/ α_2 -agonists, there may be a net reduction in ischaemic events and short- as well as long-term cardiovascular complications. However, this hypothesis must be evaluated in future randomized clinical trials. A combin-

ation of β -AAs with α_2 -agonists appears to be less meaningful except for α_2 -agonists being administered by the intrathecal or epidural route. An increased incidence of bradycardia and hypotension was reported previously for mivazerol and dexmedetomidine alone,^{46,77} which may be enhanced by co-administration of β -AAs. The combination of β -AAs and α_2 -agonists is further complicated by the following additional observations. Co-administration of clonidine and sotalol annihilates the hypotensive effects and rather increases arterial pressure, whereas propranolol and atenolol potentiate the hypotensive and bradycardic effects of clonidine in hypertensive patients.³⁹ Notably, atenolol even more profoundly reduces arterial pressure than the non-selective propranolol. Administration of prazosin (selective for α_1 -ARs) with clonidine further reduces arterial pressure, but does not affect heart rate. While clonidine is able to antagonize β -AA withdrawal, β -AAs may be dangerous in treating α_2 -agonist withdrawal (pressure raising effect of β -AAs during clonidine withdrawal). Collectively, there is currently no evidence to combine anti-adrenergic treatments in perioperative medicine except for regional anaesthetic techniques with β -AAs or mostly intrathecally administered α_2 -agonists. Because of the simplicity, safety, and their profound impact on basic physiological mechanisms in the heart, β -AAs remain the first choice for prevention of perioperative adverse cardiac events.

Conclusions

Selective stimulation of adrenergic receptor subtypes exerts beneficial or detrimental effects on the myocardium. Fine-tuning of the complex adrenergic signalling mechanisms may provide maximal cardioprotection. α_2 -Agonists non-selectively decrease sympathetic tone, whereas β_1 -AAs may be more selective. Unfortunately, no subtype-selective α_2 -agonists are clinically available. Regional anaesthetic techniques combine effective pain relief with inhibitory but rather unpredictable effects on sympathetic nerve activity. Administration of β_1 -AAs has been proven to be most effective to prevent perioperative adverse cardiac effects. However, there is currently no 'sun and centre' in the present armamentarium of perioperative sympatho-modulatory treatments. Only a detailed understanding of the complexities of adrenergic signalling and intracellular Ca^{2+} handling as well as of relevant genetic polymorphisms will lead to novel more effective therapeutic strategies in perioperative medicine.

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