Analgesic Control During Acute Pain to Protect Heart Function

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Abstract

Pain activates a general hormonal and inflammatory reaction is a main determinant in post-surgical patient's recovery that may negatively affect the CV system, especially in high-risk patients. Pain can also become chronic, increasing the risk for CV dysfunctions.

Epidural analgesia has various beneficial effects on patient's outcome, including the reduction of stress response and sympathetic activation after surgery. Some data suggest a protective role of EA on CV morbidity, especially on ischemia and dysrhythmias. However, serious CV complications may be expected with neuraxial anesthesia.

Traditional CV drugs such as alpha-2 agonists and beta-blockers display important role in pain treatment. Clonidine may also protect from CV morbidity perioperatively, by improving hemodynamic and sympathetic stabilities and

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reducing stress response, while beta-blockers display beneficial effects in cardiac surgery but may be deleterious in noncardiac surgery.

On the other hand, common drugs that are effective for analgesia may also improve the risk for CV morbidity. COX-2 inhibitors are contraindicated for chronic use in pain patients; however, they may not be unsafe in the perioperative setting. Available data are sparse to conclude that short-time administration of COX-2 inhibitors in the perioperative setting is associated to higher risk of CV morbidity, except for patients at higher risk for cardiac events. As well, new data suggest that acetaminophen, which is traditionally considered safe in terms of CV risk, may not be as safe as believed. Opioids are safe, but can harm CV homeostasis in specific cases or when associated with other drugs; neuraxial opioids may protect from hemodynamic impairment and positively affect analgesia.

Protecting heart function during pain flares means acting on nociceptive stimulus and on the organic response to pain; the concept should be to stabilize and bring homeostasis to a pain patient's CV system, always balancing beneficial and detrimental effects of any treatment.

Keywords

Postoperative analgesia · Surgical outcome · Surgical stress · Cardiovascular complications · Myocardial infarction · Stroke · NSAIDs · Acetaminophen · Alpha-2 agonists · Beta-blockers

Introduction

Pain has negative impact on the cardiovascular (CV) system and the heart, and complications may occur in acute pain patients, as well as in chronic pain patients, who experience a severe pain flare. Hormonal and metabolic changes immediately follow surgical trauma, with a wide range of endocrine, immunological, and hematologic effects, which are primarily activated by afferent neural inputs from the injured area [1]; tissue injury is responsible for the inflammatory reaction and physiologic stress response observed during the perioperative period [2].

This inflammatory reaction has a major influence on a patient's recovery trajectory since it is involved in a variety of adverse outcomes besides acute pain [3]: fatigue and delirium, cardiovascular and thromboembolic events, metabolic deregulation (i.e., insulin resistance or activation of a catabolic state), and immune impairment [1]. This is the so-called surgical stress syndrome that was therefore identified as the main determinant of perioperative morbidity in various surgical settings [4].

One of the goals of intra- and postoperative analgesia should be to minimize the effect of surgical stress, including the effects on heart and CV function, meaning to stabilize and bring homeostasis to a pain patient's CV system. This is particularly the case in older patients, who display either previously diagnosed or unknown CV disease, or who may be at higher risk of developing it.

Pain Pathways and Nociception

Nociceptors are the specialized sensory receptors responsible for the detection of noxious stimuli, transforming the stimuli into electrical signals, and then conducting them to the central nervous system (CNS). Distributed throughout the body, they can be stimulated by mechanical, thermal, or chemical stimuli. Inflammatory mediators are released from damaged tissue and can activate nociceptors by reducing the activation threshold: this process is called *peripheral sensitization*.

Nociceptors are the free nerve endings of primary afferent Aδ and C fibers; the so-called *nociceptive* fibers that are mainly responsible for acute postoperative pain are as follows:

- Aδ fibers are lightly myelinated. They respond to mechanical and thermal stimuli, carrying rapid, sharp pain. They are responsible for the initial reflex response to acute pain, especially to dynamic stimuli.

- C fibers are unmyelinated and are also the smallest type of primary afferent fiber. Hence, they demonstrate the slowest conduction. C fibers are polymodal, responding to chemical, mechanical, and thermal stimuli, leading to slow, burning pain.

Aδ and C fibers synapse with *secondary afferent neurons* in the dorsal horn of the spinal cord. Primary afferent terminals release a number of excitatory neurotransmitters, and complex interactions occur in the dorsal horn between afferent neurons, interneurons, and descending modulatory pathways. These interactions determine activity of the secondary afferent neurons. The pathways interacting in this complex network may be schematically divided in ascending (excitatory) and inhibitory (spinal and supraspinal) pathways.

Ascending pathways carry nociceptive signals to higher centers in the brain: secondary afferent neurons ascend in the contralateral thalamus; *third order neurons* then ascend to terminate in the somatosensory cortex. However, the experience of pain is complex and subjective, and is affected by factors such as cognition (distraction or catastrophising), mood, beliefs, and genetics. The somatosensory cortex is important for the localization of pain, but projections to the periaqueductal gray matter (PAG) and other important structures in the CNS exist. Imaging techniques such as functional magnetic resonance imaging have demonstrated that a large brain network (often called the "pain matrix") is activated during the acute pain experience [5]: the commonest areas activated include the primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortex, and the thalamus, demonstrating that these areas are all important in both the discriminative and emotional aspects of pain perception.

Meanwhile, other mechanisms act to inhibit pain transmission at the spinal cord level. These mechanisms are characterized by descending inhibition from higher centers. Two of them deserve special attention:

- Gate control theory (GCT) of pain: GCT describes a process of inhibitory pain modulation at the spinal cord level. It explains why when we hurt any part of our body, it feels better when we rub it. By activating Aβ fibers (non-noxious, myelinated fibers responsible of pressure and tactile sensation) with tactile, non-noxious stimuli inhibitory interneurons in the dorsal horn are activated leading to inhibition of pain signals transmitted via C fibers.
- Descending inhibition: the periaqueductal gray in the midbrain and the rostral ventromedial medulla (RVM) are two important areas of the brain involved in descending inhibitory modulation. Descending pathways project to the dorsal horn and inhibit pain transmission. These pathways are monoaminergic, utilizing noradrenaline and serotonin as neurotransmitters, as well as high concentrations of opioid receptors and endogenous opioids.

Pain pathways are also connected with the autonomic system, and such relationship is the main mechanism underlying CV morbidity.

The Autonomic Nervous System (ANS)

The autonomic nervous system is a control system that acts largely unconsciously and regulates body functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. Within the brain, the autonomic nervous system is mainly regulated by the hypothalamus.

The autonomic nervous system is divided into the *sympathetic* nervous system and *parasympathetic* nervous system. The sympathetic nervous system is often considered the "fight or flight" system, while the parasympathetic nervous system is considered the "rest and digest" system. In many cases, both of these systems have "opposite" actions where one system activates a physiological response and the other inhibits it.

Both systems coexist in a steady state, which can be altered by both pain and anesthetic techniques. Once pain stimuli reach the CNS, a stress reaction is triggered via the hypothalamic–pituitary–adrenal (HPA) axis; the autonomic system is therefore unbalanced toward a sympathetic activation, mainly mediated by the increased catecholamine's

production. Efferent messages can trigger changes in different parts of the body simultaneously, especially influencing CV function (see below).

As well, neuraxial administration of anesthetic compounds (especially local anesthetics) can block pre- to postganglionic communication in paravertebral ganglia, reducing sympathetic tone and unbalancing the system toward the parasympathetic component.

Both mechanisms underlie a loss-of-balance that may favor some CV side effects and complications.

Effects of Pain on Cardiovascular System

Pain influences the CV system by multiple mechanisms, and also affects other physiologic pathways that are involved with CV morbidity.

Pain causes elevation of *blood pressure* and *pulse rate* by two basic mechanisms that may simultaneously operate [6–11].

The sympathetic (autonomic) nervous system is stimulated by electrical pain signals that reach the central nervous system. Pain activates the hypothalamic–pituitary–adrenal axis: adrenocorticotropin hormone (ACTH) is released centrally, which stimulates the adrenal glands to release adrenalin with subsequent elevation of pulse rate and blood pressure [12]. A hallmark complication of uncontrolled pain is vasoconstriction due to increased sympathetic tone, as well. A step-up in heart rate and blood pressure due to autonomic sympathetic stimulation can be a terminal event in a patient who has existing heart disease or vascular compromise.

Recognition of sympathetic stimulation is a useful clinical tool to guide therapy and diagnose uncontrolled pain. Besides hypertension and tachycardia, sympathetic discharge also produces mydriasis (dilated pupil), diaphoresis (sweating), hyperactive reflexes, nausea, diarrhea, vasoconstriction (cold hands and feet), anorexia, and insomnia.

Protecting the CV system during pain requires to block (or at least reduce) the elevation of heart rate and blood pressure stimulated by pain, especially in patients at risk or with reduced functional reserve.

Persistent Pain May Affect CV Morbidity

Usually acute postoperative pain is supposed to resolve in a variable timespan according to the type of surgery. However, pain can sometime last longer than expected, and configure the so-called persistent postsurgical pain (PPSP). Some patients can experience pain for months or year after surgery, leading to reduction in the quality of life and patient's performance [13].

Persistent postsurgical pain (PPSP) probably relies on a dysfunction of the mechanisms underlying secondary hyperalgesia and sensitization [14]. Physiologic, adaptive, and typically *transient* modifications within the central nervous system (CNS) in response to pain stimulus becomes *permanent*, leading to a persistent state of activation within the CNS, which becomes constantly hyperreactive [13]. At present, the cause of this dysfunction is not known, as well as why only some patients develop PPSP while others do not. However, some patients (even with heart or vascular comorbidities) can develop persistent pain after surgery: the aberrant, neuroanatomic changes that may occur with constant pain appear to be capable of producing *continuous sympathetic discharge* [15–17].

Some intractable pain patients have chronic tachycardia. The apparent cause is continuous sympathetic discharge from rearranged neural anatomy, which imbeds the memory of pain in its circuitry [15–17]. Despite aggressive opioid and other treatments – such as antidepressants or benzodiazepine – the tachycardia may not abate. Severe fibromyalgia patients are particularly prone to this phenomenon.

The relationship between hypertension and chronic pain is still not clear, but pain and cardiovascular modulatory pathways are overlapped and connected [18–20]. Some studies on chronic pain patients have reported a positive correlation between blood pressure and pain sensitivity in chronic pain conditions, as well as an increased

prevalence of hypertension in chronic pain population [21], suggesting chronic pain as a risk factor for hypertension [18]. Recent data further argue in favor of a high blood pressure-pain intensity association, with hypertensive patients being more prone to suffer higher levels of PPSP [22], reflecting a pathologic, maladaptive mechanism in the common adrenergic pathway (pain and blood pressure), leading to hypertension and central sensitization (and persistent pain).

Chronic pain states are known to raise serum lipids [23, 24]. Although the mechanism is somewhat unclear, serum cortisol elevations occur during uncontrolled pain and elevated cortisol is known to elevate serum lipids and glucose. Finally, drugs used for chronic pain management, like NSAIDs or Opioids, are associated with consistent (including CV) side effects.

Since uncontrolled postoperative pain is one of the main risk factors for PPSP, effective acute pain control may reduce CV morbidity besides the immediate perioperative period, by reducing the negative impact of chronic sympathetic discharge and pain medications.

Analgesic Strategies and Their Effect on CV Morbidity

The aim that should be always pursued to protect the CV system from pain is to provide effective analgesia. Effective acute pain treatment should be based on multimodal analgesia (different drugs aimed to different mechanisms that create and maintain pain are used in order to improve effectiveness and reduce side effects). Multiple drugs and techniques are used for this purpose that can be variously combined; however, some of them are worth to be mentioned in the perspective of heart protection (namely regional anesthesia with local anesthetics and alpha-2 agonist clonidine), because they are associated with specific beneficial effects for the CV system. On the other hand, some of them deserve special attention, since they are largely used in clinical practice because of their efficacy, but also display potential side effects on heart function and CV morbidity (NSAIDs and acetaminophen, beta-blockers).

Regional Anesthesia and Local Anesthetics

Regional anesthesia (RA) involve segmental block of a specific body region according to the source of pain. RA can be performed at the neuraxis, by administering a mixture of local anesthetics (LA) (and eventually adjuvants) in the epidural space (epidural analgesia) or in the subarachnoid space within the CSF (spinal anesthesia). Nevertheless, anesthetic mixture can also be placed on specific points along peripheral nerve's course, configuring the so-called peripheral nerve blocks. Both strategies can be prolonged over time with catheters insertion, allowing continuous regional anesthesia.

Regional anesthesia is considered as the "gold-standard" analgesic technique in many surgical settings, due to the ability of providing strong blockade of pain signals and leading to a wide range of benefits. RA globally preserves the homeostasis comparing to other analgesic approaches, and is a major item in "fast-track" methodologies to reduce perioperative complications and enhance patients' recovery after surgery [25]; many data suggest that RA is generally associated with improved short- and long-term outcome in patients receiving surgery [26, 27].

RA can modulate the stress response mainly by: (1) the direct anti-inflammatory effect of local anesthetic and (2) the effective block of neural afferents and sympathetic activation.

Local anesthetics (LA) are a major component of RA techniques and display some direct and indirect anti-inflammatory properties. Interruption of nociceptive transmission by sodium channel blocking reduces "neurogenic inflammation" (i.e., the release of inflammatory mediators by stimulated neurons); the interruption of neurogenic inflammation modulates both peripheral and central sensitizations processes as local neurogenic inflammation contributes to the general inflammatory response [28].

Neuraxial anesthesia provides an effective block of neural afferents and reduces sympathetic activation in response to pain; further, the administration of LA in the spinal canal at thoracic level provides sympathetic block directly on the

thoracic sympathetic trunk. Sympathetic blockade and lower activation in response to pain by neuraxial anesthesia reduces myocardial oxygen demand and improves myocardial oxygen supply by coronary dilatation [29–31]; thoracic epidural analgesia (TEA) also directly reduces pulmonary vascular resistance in pulmonary hypertension [32]. Recent data on chronic patients with dilated cardiomyopathy show that epidural infusion (when combined with conventional medical treatment) may reverse myocardial fibrosis and improve cardiac function [33].

Available data on the protective effect of regional anesthesia on CV morbidity are sparse and far from giving conclusive evidence. However, some initial suggestions of benefits coming from the adoption of RA are available, especially regarding the occurrence of myocardial ischemia.

Some data show that cardiac morbidity was generally lower among patients treated with epidural analgesia. A recent meta-analysis, including 11 randomized studies and involving 1173 patients [34], showed a significant reduction in perioperative myocardial infarction in patients treated with thoracic epidural analgesia in comparison with control groups. A Cochrane study in 2016 from a review of 15 clinical trials concluded that epidural analgesia significantly reduces the number of people who suffer heart damage, and improves other important perioperative outcomes, including time to return of unassisted respiration, gastrointestinal bleeding, and ICU length of stay, but without reducing death rates at 30 days [35]. When considering ischemic patients undergoing elective major abdominal cancer surgery, Mohamed et al. concluded that lumbar epidural anesthesia combined with general anesthesia provided better pain relief, but ischemic cardiac events were similar in both groups [36].

In agreement with previous data, a very recent randomized controlled trial [36] added additional evidence that perioperative thoracic epidural analgesia reduces cardiac events in patients suffering from coronary artery disease and subjected to major surgery; a significant reduction in overall adverse cardiac events (myocardial injury, arrhythmias, angina, heart failure, and nonfatal cardiac arrest) was observed in patients receiving epidural analgesia, and there was a significant reduction in intraoperative mean arterial pressure and heart rate.

Dysrhythmias are also common complications in the immediate postoperative period, even more common after upper abdominal and thoracic surgeries. The occurrence of arrhythmias can be explained by many factors such as preexisting cardiac pathology, intraoperative events, and arrhythmia triggers. Autonomic imbalance after operation has been implicated as a possible trigger, and is thought to be characterized by increased sympathetic tone and lower vagal tone [37].

The first randomized evaluation of the impact of perioperative epidural analgesia on outcome in a large series of 400 patients with normal ventricular function undergoing coronary artery bypass grafting showed a reduction in the incidence of supraventricular arrhythmias [38]. In this study, epidural analgesia resulted in a better optimization of heart rate and mean arterial pressure during the intra- and postoperative period in comparison with intravenous anesthesia. This result showed the advantage of epidural analgesia by means of decreased heart rate and improved coronary blood flow.

However, results from further trials have provided conflicting evidence: methodological bias or discrepancies between studies may account for nonuniform results.

Kessler et al. compared heart rate either with or without TEA during coronary artery bypass grafting performed on a beating heart and reported that HR with TEA was lower than preoperatively, during sternotomy and anastomosis. In that study, esmolol was administered in the group that received GA because of a high HR.

Kopeika et al. showed TEA provided superior postoperative pain control than intramuscular opioid administration after pulmonary resection, and found only a “tendency” of less frequent postoperative atrial fibrillation among those who received TEA [39].

Oka et al. compared TEA with bupivacaine and TEA with morphine for postoperative analgesia for pulmonary resection and found that occurrence of atrial fibrillation and supraventricular tachycardia within 3 days after surgery was less

for TEA with bupivacaine [40]. This should reinforce the concept of high sympathetic block as the major protective mechanism from arrhythmias, but this study was biased by the fact that patients in the bupivacaine group received a higher dose of indomethacin than those in the morphine group.

In a recent study, the occurrence of atrial fibrillation, atrial flutter, and supraventricular tachycardia increased after the TEA catheter was removed; however, TEA was continued only until 2–3 days after surgery, which is the time of frequent occurrence of atrial arrhythmia [41], and the occurrence of atrial arrhythmia after discontinuation of TEA could be just coincidence rather than a causal relationship.

Other studies have even displayed conflicting evidence, suggesting that TEA may be not protective (or even harmful). Jiang et al. compared the incidence of supraventricular arrhythmia within 48 h after pulmonary resection between patients having TEA with a combination of local anesthetic and opioid for intra- and postoperative analgesia and those who received intravenous patient-controlled analgesia with opioids. These authors observed significantly less supraventricular tachycardia and a tendency of less frequent atrial fibrillation among patients who received intravenous patient-controlled analgesia [42]. Ahn et al. compared intravenous patient-controlled analgesia with fentanyl plus ketorolac vs TEA for postoperative analgesia among esophageal surgery patients and found that the occurrence of arrhythmia until 3 days after surgery was similar between the groups [38]. Conversely, TEA was not associated with reduced occurrence of postoperative atrial arrhythmia in other studies [43]. Apart from differences in the populations and the specific analgesic regimens studied, differences in the way arrhythmia was diagnosed, duration of observation after the surgery, and use of nonsteroidal anti-inflammatory drugs, which are potentially protective against atrial arrhythmia, could be possible explanations of conflicting outcomes [43].

Despite the possible beneficial outcomes, immediate CV side effects are related with the use of neuraxial anesthesia. The preganglionic neurons of the sympathetic system originate from the thoracolumbar region of the spinal cord (T1 to L2–L3), and travel to paravertebral ganglia, where they synapse with a postganglionic neuron. The physiologic effects of neuraxial anesthesia are the result of blockade of sympathetic component, the compensatory reflexes, and of unopposed parasympathetic tone.

Hypotension occurs as a result of a decrease in systemic vascular resistance and peripheral blood pooling with decreased venous return to the heart, or both. In addition, block of cardio-accelerator nerve fibers (originating from T1 to T4 nerve roots) with high subarachnoid block can contribute to hypotension through a decrease in heart rate and cardiac output. Mechanisms for bradycardia are direct (blockade of sympathetic cardio-accelerator fibers) and indirect. Indirect mechanisms include decreased output of the myocardial pacemaker cells due to decrease in venous return, stimulation of low-pressure baroreceptors in the right atrium and vena cava, and stimulation of mechanoreceptors in the left ventricle resulting in bradycardia (paradoxical Bezold-Jarisch reflex). Hypotension and bradycardia are frequent during neuraxial anesthesia and can eventually evolve in major events such cardiac arrest. Some patient populations are at higher risk, because of either higher sensibility to local anesthetics/high spinal block or because of coexisting comorbidities leading to a dramatic decrease in cardiac output (elderly, pregnant women, hypovolemic patients, patients with major mitral or aortic stenosis, pulmonary hypertension, low cardiac output, and/or hypertrophic left ventricle).

Peripheral nerve blocks are a valuable alternative for patients at risk of complications with neuraxial anesthesia: since they are performed away from the neuraxis, the impact on sympathetic tone and CV homeostasis is far less pronounced, except in case of rare complications associated with specific nerve blocks. Such complications are mainly related to the migration of local anesthetics to the neuraxis or to local anesthetic systemic toxicity (LAST).

Epidural or intrathecal spread during lumbar plexus blocks is often observed but is rarely clinically significant; however, unintended neuraxial block can lead to cardiac or respiratory arrest

[44]. This is one of the most feared complications for anesthesiologists; since it is unpredictable and there are no validated strategies to avoid it, alternative techniques are often used and suspicion is always maintained when a lumbar plexus block is performed [45].

LAST results from intravascular injection or from massive reabsorption of local anesthetics. It has variable presentation, but encompasses neurologic symptoms (tinnitus, lightheadness, perioral numbness, peripheral tremors up to seizures in severe cases) and/or CV symptoms (arrhythmias up to ventricular fibrillation and cardiac arrest). Specific guidelines are available for treatment, while specific approaches are adopted to avoid LAST (ultrasound guidance, use of lower doses of local anesthetics, intermittent aspiration before injection, epinephrine as marker of early intravascular injection) [46].

Except for these rare events, the impact of hypotension, bradycardia, or major adverse CV complications is reduced with the use of peripheral techniques.

Clonidine and Beta-Blockers

Clonidine is a centrally acting imidazolin α2-adrenergic agonist, analog of norepinephrine. The presynaptic stimulation of α2-receptors is coupled via G-protein to several effectors including inhibition of adenylate cyclase and effects on potassium and calcium channels that finally restricts the release of norepinephrine in the central nervous system. This drug has been largely studied in anesthesia, suggesting a place for analgesia, antiemesis, bleeding reduction, induction time reduction, hemodynamic and hormonal stability, reduction of oxygen consumption, renal protection, anesthetics-sparing effect, anxiolysis, sedation, antishivering, recovery time reduction, and myocardial protection.

Evidence from metanalysis on 57 studies and nearly 15,000 patients shows that clonidine has several protective effects on heart function in the perioperative period: generally speaking, clonidine improves hemodynamic and sympathetic stabilities [47].

Clonidine is a well-known analgesic, which helps reducing postoperative pain; furthermore, clonidine attenuates blood pressure and heart rate increase after intubation and insufflation, that are key moments in anesthesia and during laparoscopic surgery (which is increasingly adopted in clinical practice): sympathetic activation may be deleterious, and heart rate and blood pressure stability is helpful, especially in patients with previous CV morbidity and higher risk for complications when CV homeostasis is not carefully maintained. Despite result being less clear, some studies also claim a role for clonidine in reducing epinephrine release and stress response after surgical manipulation, as well as oxygen consumption, with the cumulative result to reduce perioperative metabolic demands [47]. Clonidine can also be used as an adjuvant to local anesthetics in neuraxial anesthesia. Epidural clonidine demonstrates greater anti-inflammatory effects in terms of reduction in systemic pro-inflammatory cytokine expression than local anesthetics [48, 49].

A recent RCT has questioned the role of clonidine in reducing myocardial infarction [50], but data on this specific outcome are sparse and methodological discrepancies hinder any firm conclusion on the topic [47].

In contrast, it is important to keep in mind that nonfatal bradycardia/nonfatal cardiac arrest and hypotension have been described with the use of clonidine. Despite no report of sequels, it should be assumed that not enough data concerning bradycardia/nonfatal cardiac arrest are available to formally conclude about their safety. However, clonidine-induced hypotension has not been specifically described to be associated with adverse events linked to hypotension (worse renal or cardiac outcomes). Even if not formally demonstrated by available large-scale data, hypotension due to other factors than clonidine (e.g., hypovolemic shock) is problematic, but not necessarily if specifically due to clonidine, and clonidine can be considered as safe. Further, findings are compatible with the belief that α2-adrenergic agonists depress baseline sympathetic activity but that clonidine leaves, at least partially, unaffected the response to environmental or circulatory challenges such as hypotension [51].

Of course, clonidine should be used carefully used in the elderly patient [52], as in predicted hypotensive response as after tourniquet deflation [53], and considering the different impact on heart rate and blood pressure according to the route of administration (being more likely associated to hypotension and bradycardia when injected in the neuraxis rather than systemically) [54]. Beta-blockers are drugs that attenuate stress response, as well, which results in reduced heart rate and blood pressure. These effects are desirable to fight the stress response, but if pronounced, they may cause very low blood pressure, a very low pulse, and ultimately stroke or death.

Beta-blockers are extremely effective as analgesics: a systematic review and meta-analysis investigating the effect of beta-adrenergic antagonist on perioperative pain in RCTs showed that perioperative esmolol and propranolol decrease postoperative pain and analgesic consumption when given as an adjuvant to general anesthesia. Adverse effects were rarely reported in RCTs, but notably, most of them were cardiovascular alterations [55].

A large Cochrane review on 88 randomized controlled trials with 19,161 participants recently gave more detailed clues on the risk/benefit profile of this class of drugs. Data show that perioperative application of beta-blockers still plays a pivotal role in cardiac surgery, as they can substantially reduce the burden of supraventricular and ventricular arrhythmias in the postoperative period. Their influence on mortality, myocardial infarction, stroke, congestive heart failure, hypotension, and bradycardia in this setting remains unclear [56].

However, evidence shows opposite relationship between beta-blockers and CV outcomes in noncardiac surgery, namely an association of beta-blockers with increased all-cause mortality. Data from trials further suggest an increase in stroke rate. As the quality of evidence is still low to moderate, more evidence is needed before a definitive conclusion can be drawn; however, the beneficial reduction in supraventricular arrhythmias and myocardial infarction in noncardiac surgery seems to be offset by the potential increase in mortality and stroke [56].

NSAIDs and Acetaminophen

NSAIDs and Acetaminophen/Paracetamol are extensively used in clinical practice, and are a cornerstone for postoperative analgesia in nearly all surgical setting. Despite the undisputed efficacy, all of them have potential side effect that may limit their use in some clinical situations. Side effects are a concern both when they are administered chronically or for few days in the immediate postoperative period.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

All of NSAIDs' side effects are associated with the intrinsic ability of this class of drugs of blocking cyclooxygenase activity: Cyclooxygenase-1 (COX-1 – innate) and Cyclooxygenase-2 (COX-2 – induced by surgical stimulus).

COX-1 and COX-2 inhibitors are both effective as analgesics, but COX-2 selective inhibitors have been introduced because of their higher selectivity on trauma-induced COX, with reduced platelet impairment and being less aggressive on gastric mucosae.

Traditionally, NSAIDs main side effects were considered to be gastric toxicity, bleeding, and kidney failure. However, new interest has emerged in the last 10 years on the potential CV risk associated with NSAIDs, especially with selective COX-2 inhibitors.

Several explanations of CV toxicity have been proposed. The more likely theory is that the inhibition of COX-1 and COX-2 induces an unbalance between thromboxane (TXA) and the prostaglandin (PGI2) production: platelet TXA production is not inhibited if COX-1 activity is not completely blocked, while the production of endothelial PGI2 is suppressed by COX-2 inhibition. PGI2 is a powerful inhibitor of platelets aggregation and a potent vasodilator, while thromboxane is a potent vasoconstrictor and induce platelet aggregation.

Cardiovascular side effects have however been reported after a long period of selective COX-2 inhibitors, but it is not clear if the administration for few days can be harmful, as well.

Furberg et al. [57] evaluated the incidence of cerebrovascular accidents in patients undergoing

coronary artery bypass graft (CABG) and showed a three-fold higher risk of cardiovascular events compared with placebo [57]. These data have, however, not been confirmed in a recent study: 1,065 patients undergoing thoracic and cardiovascular surgery were treated with different nonselective NSAIDs, particularly diclofenac, ketorolac, and indomethacin. No difference in side effects was found between NSAIDs-treated patients and the control group [58]. The short duration of drug administration and low risk patients may have influenced the lack of cardiovascular and renal side effects. On the other hand, in a recent cohort study that has enrolled 83,677 patients the use of NSAIDs in patients with prior myocardial infarct resulted in an increased risk of death and recurrent myocardial infarction also if the drugs are used for short time [59]. Taken together, these data may suggest that the higher risk of CV toxicity may be limited to high-risk patients, i.e., patients with prior CV morbidity.

However, the current idea that a great difference in CV risk exists between combined NSAIDs (COX-1 + COX-2) and COX-2 selective inhibitors should be revisited. Nonselective NSAIDs inhibit both COX-1 and COX-2 enzymes; selective COX-2 inhibitors still act on both COX isoforms, but producing lower effect on COX-1. For this reason, difference in cardiovascular risk between the two drugs is more hypothetical than real.

As abovementioned, the CV adverse profile is related with the degree of TXA synthesis and PGI inhibition: a reduction in TXA production greater than 95% produces cardiovascular protection as low-dose aspirin does. The incomplete block of TXA production provided by COX-2 selective inhibitors, as well as by many nonselective NSAIDs does not reduce TXA production in significant percentage, predisposing to CV complications, regardless of the type of NSAIDs and their selectivity [60]. The increase in CV risk not only depends on the TXA/PGI2 inhibition ratio, but also on other mechanisms (including blood pressure elevation and COX-independent mechanisms) [61]; available clinical data indicate that the entire substance group of NSAIDs may cause a little but increased risk for cardiovascular/thromboembolic events [62], independently on COX-1/-2 selectivity.

Most of data about toxicity are drawn from chronic patients, which are administered with NSAIDs for a long period of time. Projecting the same results on acute pain patients, i.e., those receiving NSAIDs for a brief timespan (days) after surgery, may lead to wrong conclusions. Actually, few studies exist on NSAIDs-associated CV risk in patients treated for postoperative pain according to COX selectivity.

The administration of paracoxib and valdecoxib in the immediate postoperative period of coronary surgery increased the risk of cardiovascular events (risk ratio 3.7 [63]). However, the nonselective NSAIDs ketorolac, when administered in the postoperative period of cardiac surgery has not showed an increase of cardiovascular risk [64]. As for previous data, COX-2 selective inhibitors only showed to increase CV side effects in high-risk patients with previous CV comorbidities. No significant increase in the incidence of postoperative myocardial infarction was retrieved in more than 10,000 patients undergoing total joint replacement: 0.8% for patients that received meloxicam or ketorolac, 1.3% for patients that received celecoxib, and 1.8% in subjects who does not receive NSAIDs [65].

Data on postoperative patients are somewhat conflicting; however, given the best available evidence, the European Medicine Agency Committee for Medicinal Products for Human Use decided that COXIBs but not nonselective inhibitors should be contraindicated in patients with cardiovascular disease [66]. The possible increase of cardiovascular adverse events has been receipted by the Food and Drug Administration that stated that, in the characteristics of the drugs, a boxed warning about the risk of cardiovascular disease is reported.

Noteworthy, most of data are transferred from the chronic pain population to the completely different setting of acute pain; further, when considering postoperative pain patients, a distinction should be made for noncardiac and cardiac surgery (where the risk for CV major events is probably mostly not related to the type of patient and surgery, but rather to NSAIDs administration).

Currently, despite unclear evidence existing on NSAIDs CV toxicity for short-time administration (perioperatively), the most rational approach for acute pain seems to base the choice of NSAIDs on the type of patient and surgery that we are dealing with. Patients with no CV comorbidities can be treated with both selective and non-selective drugs; when gastric toxicity/bleeding are feared, COX-2 inhibitors are probably the better choice, while it should be avoided in patients with higher risk for cardiac events (due to the type of surgery or to patient's medical history comorbidities) [67, 68].

Acetaminophen/Paracetamol

Paracetamol is the most widely used over-the-counter and prescription analgesic worldwide [69]. It is the first step on the WHO pain ladder and is currently recommended as first-line pharmacological therapy by a variety of international guidelines for a multitude of acute and chronic painful conditions, including multimodal analgesia for mild to severe postoperative pain. Irrespective of its efficacy, paracetamol is generally considered to be safe than other commonly used analgesics such as nonsteroidal anti-inflammatory drugs [70, 71].

However, the analgesic benefit of paracetamol has recently been called into question in the management of chronic painful condition (like osteoarthritis) [72], and a recent systematic review of studies investigating the association between paracetamol and major adverse events in the general adult population gave clues on the unexpected paracetamol-associated CV toxicity [73]. Comparing paracetamol use versus no use, a dose–response and an increased relative rate of mortality was reported in patients receiving paracetamol [74, 75]. Further, one study reporting cardiovascular adverse events showed an increased risk ratio of all cardiovascular adverse events (confirmed or probable nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, or fatal stroke) [76].

While many limitations exist to the interpretation of these results that are important to consider, the striking trend of dose–response is a consistent finding across multiple outcomes and studies. There is also evidence from the case–control literature supporting the dose–response seen in the abovementioned review, and a similar toxicity profile is demonstrated in systematic reviews of short-term RCTs [72]. However, these data come from the chronic pain population; evidence from the available literature show that adverse events associated with paracetamol in the postoperative period (in patients with short-time administration) are trivial [77].

Despite the true risk of paracetamol, prescription may be higher than that currently perceived in the clinical community for chronic pain patients; it is still a cornerstone in postoperative analgesia and should still be considered as the safest available drug in the postsurgical setting.

Opioids

Opioids bind to opioid-specific receptors that are located in the central nervous system (CNS). However, the same opioid receptors are available in many other organs, including cardiovascular tissue [78]. Opioid receptors are linked to G proteins, and activation of the opioid receptor leads to membrane hyperpolarization. Opioids may differently impact the CV system when given acutely rather than chronically [79]; in the acute and intraoperative setting, opioids can are a mainstay for surgical anesthesia and for postoperative analgesia, but they are also responsible for important side effects; some of them (nausea, vomiting, pruritus, ileus, respiratory depression) can prolong and complicate perioperative recovery. In some cases, paradoxical opioid-related hyperalgesia (associated to intraoperative or preoperative opioid use) can increase postoperative pain and analgesic consumption [80]; tolerance is a major concern, as well, and opioids in the perioperative period seem to predispose to chronic abuse [81, 82]. Opioid abuse in the pre- and perioperative period has generally been linked to poorer outcomes and higher rate of readmission [83, 84].

Opioids can also cause CV damage. Opioids administered as part of an anesthetic are thought to have modest direct effects on the heart, especially as an isolated drug. When administered

alone, opioids (other than high doses of meperidine) do not depress cardiac contractility. Intravenous fentanyl leads to minimal changes to cardiovascular function, heart rate, and blood pressure [85]. Nevertheless, while cardiac contractility may not be affected, opioids can impact other aspects of the cardiovascular system: several opioids can cause vagus nerve-mediated bradycardia. In addition, acute administration of opioids can lead to vasodilation and decreased sympathetic tone. Tramadol administration can lead to serotonin syndrome [86], which can lead to cardiac arrhythmias; cardiac side effects may range from agitation and palpitations to rhythm abnormalities, conduction defects, and cardiac arrest [87]. Morphine, hydromorphone, hydrocodone, and meperidine can lead to histamine release, and as a result can cause significant decreases in systemic vascular resistance and blood pressure, which may require the administration of vasopressors and intravenous fluids. However, opioids are rarely the sole anesthetic agent used, and when combined with other medications they are associated with significant changes in cardiac function. When administered with benzodiazepines, opioids can significantly decrease cardiac output, and significant CV effects can be observed when opioids are administered with inhaled anesthetics.

Opioids have been found to have minimal effect on coronary vessel vasomotor tone. Studies on the influence of opioids on perioperative ischemia have suggested that they can mimic ischemic preconditioning, reducing infarct size. Mechanisms are not completely understood, and opioid-based anesthesia has not been shown to reduce intraoperative ischemia, postoperative myocardial infarction, or death [88].

Finally, opioids can be given into the neuraxis, either by epidural and intrathecal route. In these cases, they are administered as adjuvants to local anesthetics: morphine, fentanyl, and sufentanyl have all demonstrated to prolong sensitive block and postoperative analgesia comparing to local anesthetics alone. Neuraxial opioids reduce the amount of anesthetics required for surgical anesthesia, and have lower effects on the sympathetic tone than local anesthetics: neuraxial opioids are a cornerstone to reduce hemodynamic impairment associated with neuraxial techniques, reducing the risk for major CV events (especially in high-risk patients). Concerns exist on other side effects (nausea, vomiting, pruritus, sedation), but neuraxial opioids are more protective than harmful on the CV homeostasis.

Conclusion

Pain has negative impact on the cardiovascular (CV) system and the heart because it activates a systemic stress response with generalized sympathetic activation. Unbalancing the homeostasis of the CV system may lead to major complications, especially in patients with previous comorbidities or risk factors.

Several drugs and techniques are available that can be combined in multimodal strategies to achieve optimal pain control. Some of them display specific advantages, while others may be associated with adverse outcomes. In some cases, evidence of risk/benefits is stronger while in other case available data should be interpreted with caution (because they are extrapolated from chronic pain patients and no distinction is made according to the type of surgery).

However, further studies are recommended because current data suggest, at least, that even short-term administration of specific drugs, as well as the perioperative adoption of specific analgesic strategies may influence CV morbidity, especially in high-risk situations.

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