Opioids and protection against ischemia-reperfusion injury: from experimental data to potential clinical applications

G. MINGUET, J. F. BRCHANT and J. JORIS

Abstract: Ischemic preconditioning, first demonstrated in animal myocardium, is an intrinsic and ubiquitous mechanism of marked protection against ischemia. Accumulating evidences have established that endogenous opioid peptides and their receptors play an important role in this adaptive phenomenon in the heart and other major organs. Of interest for therapeutic developments, opioid receptor agonists have been administered successfully to improve tolerance against experimental ischemia-reperfusion in various tissues. Recent human studies now raise the possibility to exploit this opioid-induced protection in clinical cardiac ischemia. These remarkable anti-ischemic properties of opioids and their emerging potential for organ protection in perioperative medicine will be reviewed at the light of pertinent results from basic and clinical researches.

Key words: Opioids; stress response; hypoxia; ischemia; preconditioning; post-conditioning; analgesics; intravenous anesthesia.

INTRODUCTION

25 years ago, Murry and colleagues described for the first time the phenomenon of ischemic preconditioning in canine myocardium (1). Subjecting heart to brief episodes of ischemia-reperfusion before a prolonged period of ischemia resulted in a considerable reduction of the myocardial infarct size. Ischemic preconditioning elicits two consecutive windows of protection: the first one begins immediately after the preconditioning ischemia and lasts for approximately 2 hours (early or classical preconditioning), and is followed 24 hours later by a second phase (delayed or late preconditioning) lasting for approximately 72 hours (2). The efficacy of preconditioning at reducing irreversible ischemic damage and its potential for clinical applications has generated tremendous interest, as shown by the numerous studies published during the recent years.

THE NEED FOR ALTERNATIVES TO ISCHEMIC PRECONDITIONING

Ischemic preconditioning, by which a short ischemic stress can elicit tolerance to subsequent infarction, appears in itself a simple concept but its implementation in clinical practice is confronted with several limitations. Indeed, the preconditioning ischemia requires an easy and safe access to the main feeding artery at the organ of interest. As for instance, myocardial ischemic preconditioning would require surgical dissection and clamping of coronary arteries (i.e. during open heart surgery) or percutaneous endocoronary occlusion (i.e. during coronary angiography). However, in numerous clinical conditions, such vascular occlusion is not convenient and/or carries unacceptable risks such as injury to blood vessels, thromboembolic events and poor tolerance by diseased organs. In addition, efficient application of a preconditioning protocol implies that the time window of ischemia can be anticipated whereas, in real life, interruption in blood supply may arise unpredictably. For these reasons, alternatives to ischemic preconditioning have been developed.

REMOTE ISCHEMIC PRECONDITIONING

Remote ischemic preconditioning is the phenomenon by which short ischemic episodes of an
organ leads to resistance against ischemia-reperfusion in other remote organs. In clinical practice, remote preconditioning (i.e. by inducing short ischemic episodes to a limb) has been able to produce a myocardial protection similar to the one provided by local ischemic preconditioning (3). This modality of preconditioning at distance elicits numerous promises for those clinical circumstances where local preconditioning is not easily feasible to protect compromised organs (4).

**ISCHEMIC POST-CONDITIONING**

Ischemic post-conditioning consists in a reduction of reperfusion injury after prolonged ischemia using a transient interruption of blood flow during the early phase of reperfusion. Adaptive mechanisms taking place during such intermittent reperfusion reduce the infarct size as effectively as local ischemic preconditioning (5). Recently, ischemic post-conditioning has been successfully applied to humans (6). Although the possibility to reduce tissue injury after the onset of ischemia seems very attractive, this technique still needs a surgical or percutaneous vascular access.

**PHARMACOLOGICAL APPROACHES**

The signaling cascade of ischemic preconditioning involves multiple mediators such as adenosine, acetylcholine, catecholamines and opioids. These mediators are released in the extracellular space during the ischemic stress, and trigger protection by specific activation of G-protein-coupled receptors on the cell surface. Intracellular transduction and amplification of the preconditioning signal implies multiple molecular pathways, among which protein kinases play an important role. In a subsequent step, sarcolemmal and mitochondrial ATP-sensitive potassium channels (K$_{ATP}$ channels) switch to an activated open state, inducing tolerance to prolonged ischemia by a complex array of functional changes (optimized energetic status, ionic transport, gene transcription…) (2, 7). Of considerable interest for therapeutic developments, administration of several G-protein-coupled receptor agonists including opioids has shown to activate the signaling cascade of preconditioning and reproduce the ischemic preconditioning protection (8). Such pharmacological mimicking of preconditioning now represents a promising therapeutic opportunity for reducing ischemic injury in patients (9, 10). Interestingly, ischemic post-conditioning can be reproduced using comparable pharmacological means (11, 12).

**ARE OPIOIDS VALUABLE CANDIDATES TO PROTECT AGAINST ISCHEMIA-REPERFUSION INJURY?**

To answer this question, we performed a literature search for articles from 1980 to 2011, and involving the following keywords : opioids, stress response, hypoxia, ischemia, preconditioning, post-conditioning, analgesics, intravenous anesthesia. We found several experimental studies but only a limited number of human studies demonstrating a protective effect of opioids against hypoxic/ischemic injury. We preferentially selected studies published after 1995, clinical when available, using a methodology that is accessible to anesthesia practitioners, and with potential clinically relevant applications. We recognize that such a selection might have introduced some bias, but experimental data suggesting opioid-induced pre- and/or post-conditioning are so numerous that the potential protective effect of opioids cannot be discredited.

In the following paragraphs, we will have a brief overview of the physiological role of the opioidergic system in the response to stress and in the adaptation to ischemia. We will then focus on the mechanisms of opioid-induced preconditioning and post-conditioning, taking the myocardium as an example. Finally, the therapeutic potential of opioid receptor agonists as a pharmacological surrogate for ischemic conditioning to protect the heart and other major non-cardiac organs will be addressed.

**ENDOGENOUS OPIOIDS IN THE RESPONSE TO STRESS**

In the 1970’s, three major family of endogenous opioid peptides, enkephalins, dynorphins and endorphins were discovered. Since then, other endogenous opioids have been characterized (13). Endogenous opioids are released by the hypothalamo-pituitary axis in response to stress and modulate multiple adaptive mechanisms through the activation of mu (μ), delta (δ) and kappa (κ) receptors (14). In addition, during inflammation, the activation of macrophages and leukocytes further releases endogenous opioids. This inflammatory process can unmask and/or activate opioid receptors (15, 16). In this setting, endogenous opioids appear as potential natural anti-inflammatory factors. Ischemia triggers a stress response and results
in local as well as systemic inflammation, hence the question of the involvement of these endogenous opioids to limit the deleterious consequences of ischemia. An actual protective activity of endogenous opioids during ischemia-reperfusion is suggested by indirect data demonstrating that naloxone and other opioid receptor antagonists can prevent or reduce the adaptation to ischemia. This phenomenon has been extensively studied in the myocardium and is developed below.

**Opioids and Myocardial Ischaemia**

It was long known that organs of hibernating mammals can remarkably tolerate prolonged winter periods of depressed metabolism, low temperature and reduced tissue perfusion (17). Researches to elucidate the mechanisms involved in such adaptability of hibernators led to the characterization of an opioid-like 88 kDa protein from plasma that contributes to resistance against unfavorable conditions akin to cold ischemia/hypoxia (18). In addition, administration of the so-called hibernation induction trigger (HIT) protein to non hibernating animals was shown to protect their myocardium against ischemia-reperfusion injury (19). Biological effects of HIT including myocardial tolerance against ischemia could be reproduced by the δ-opioid receptor agonist D-Ala2-D-Leu5-Enkephalin (DADLE) (20). Further investigations, among which human studies, showed that myocardial ischemia results in the synthesis and release of opioid peptides from myocytes as a response to stress (21). In the 1990’s, Schultz and colleagues demonstrated for the first time that activation of opioid receptors by endogenous opioid peptides plays an important role in the ischemic preconditioning of the rat myocardium (22). This group further demonstrated that pharmacological activation of opioid receptors with morphine mimicked the cardioprotective effect of ischemic preconditioning in animals (23). There are now strong evidences that opioid receptors participate in the adaptation to ischemia in the human heart as well. During coronary angioplasty, the administration of morphine before ischemia could precondition the myocardium, resulting in the attenuation of ST segment changes (24). Conversely, naloxone abolished the protective effect of ischemic preconditioning induced by repeated balloon inflations before percutaneous coronary interventions (25). Of interest, most recent synthetic opioids commonly used for analgesia and sedation demonstrated a preconditions activity against myocardial injury in the experimental (26) and in the clinical setting (27). The clinical relevance of the beneficial properties exhibited by certain opioids is supported by a recent meta-analysis of controlled trials in cardiac surgery indicating that the use of remifentanil in the anesthetic regimen is associated with more limited perioperative myocardial injury rates (28).

**Mechanisms of Opioid-Induced Myocardial Protection**

The concept that emerges is that pharmacological activation of opioid receptors results in a protective effect, whose fundamental pathways are similar to those of ischemic preconditioning. In this setting, δ and κ receptors appear the most prominent opioid receptor subtypes for the myocardium (29, 30). The sequence of events that follows opioid receptor binding involves multiple steps of signal transduction by G-proteins (31) and intracellular protein kinases, such as protein kinase C (PKC) (32), phosphatidylinositol 3-kinase (PI3K) (33) and the mitogen-activated protein kinase (MAPK) family (34). Activated protein kinases subsequently translocate to specific targets (i.e. plasma membrane, mitochondria and nucleus) where they activate early effectors of preconditioning such as sarcolemmal and mitochondrial K<sub>ATP</sub> channels (30), concomitantly with the initiation of the late phase of preconditioning through the modulation of transcription factors and gene expression in cardiomyocytes (35).

In early preconditioning, protection conferred by sarcolemmal K<sub>ATP</sub> channel opening relies on cardiomyocyte membrane hyperpolarization, shortening of action potential, limitation of metabolic and contractile activity, and reduction of cytosolic calcium overload during ischemia. Concomitant opening of the mitochondrial K<sub>ATP</sub> channels leads to inner mitochondrial membrane depolarization, which is protective through the preservation of mitochondrial volume and homeostasis, induction of optimal conditions for ATP production, attenuation of mitochondrial calcium accumulation, and inhibition of mitochondrial permeability transition pore (MPTP) opening during ischemia-reperfusion (7, 30). Recently, the mitochondrial calcium-sensitive potassium channels (K<sub>C</sub>, channels) showed equally implicated in myocardial protection induced by ischemic and opioid-induced preconditioning (36). At the end stage of the protective cascade, closing of the MPTP, a large conductance channel in
mitochondrial membranes, seems critical to prevent a lethal cascade of membrane potential collapse, mitochondrial swelling and rupture, cytochrome C release followed by apoptosis or ATP collapse and cell necrosis (37). In addition, mitochondrial \( K_{atP} \) channel opening is linked to the production of reactive oxygen species (ROS), which act as important signaling mediators to further amplify the cardioprotective pathway through the activation by a feed back loop of the mitochondrial \( K_{atP} \) channels themselves, PKC, and multiple other specific cardioprotective elements (38, 39). It is now recognized that small bursts of ROS is a pivotal component of the protective signaling response to opioids, similarly to other forms of preconditioning. Of note, studies have reported an opioid-induced preconditioning effect, which is independent from any opioid receptor stimulation and is directly mediated by ROS formation (40).

In addition to the early phase of preconditioning that lasts some hours, opioids may elicit the delayed phase of preconditioning that lasts for several days (41). In late ischemic preconditioning, chemical signals released by the stress of ischemia, such as ROS, are transduced by signaling elements, including PKC and the nuclear transcription factor kappa B (NF-kB), to the nucleus where they initiate the transcription of various protective genes (42). Similarly, opioid administration is responsible for inducing late cardioprotection through the transcription of genes and synthesis of proteins that increase the heart tolerance against subsequent delayed ischemia. Indeed, opioids have been shown to initiate the activation of NF-kB (35) and protein synthesis associated with delayed cardioprotection. Among those proteins, the cyclooxygenase 2 (COX-2) (43), the inducible nitric oxide synthase (iNOS) (44), the 12-lipoxygenase (12-LO) (45) and the inducible heat shock proteins (HSP) can be cited (46). Subsequent acquisition of the late ischemic tolerance requires the production of several mediators, among which nitric oxide seems to play a central role (47). Finally, considerable evidence also implicates sarcolemmal and mitochondrial \( K_{atP} \) channels as effectors of the opioid-induced delayed preconditioning (48).

In remote ischemic preconditioning, the protective effect of distant tissue ischemia is consistent with the humoral nature of factors that reach the systemic circulation during reperfusion (49). Implication of circulating endogenous opioids in remote preconditioning is supported by the reversal of its myocardial protection following opioid receptor blockade (50). After reaching the systemic circulation, endogenous opioids and other humoral factors presumably activate the same intracellular signaling machinery as local ischemic preconditioning (51).

Growing evidences establish that opioids can reproduce the ischemic post-conditioning phenomenon when administered close to the reperfusion period. Morphine administered just prior to coronary reperfusion in rats showed a cardioprotective effect equivalent to that observed when morphine is administered prior to ischemia (12). This opioid postconditioning seems to share, at least partly, a common pathway with preconditioning through the modulation of protein kinase activity, activation of mitochondrial \( K_{ap} \) and \( K_{ca} \) channels, inhibition of MPTP opening, and induction of other important functional changes that optimize mitochondrial and cellular resistance against reperfusion injury (52-55). A synthetic view of the key mechanisms involved in opioid-induced protection is shown in figure 1.

**Opioid protection beyond the heart**

Protection against ischemia-reperfusion has clinical relevance beyond the heart. Numerous diseases and therapeutic procedures (i.e. cardiovascular and transplantation surgery) carry a high risk for organs to suffer from severe ischemic insults, with detrimental impact on patient outcome. Experimental studies accumulate to evidence an ubiquitous role for the opioidergic system in ischemic protection of non cardiac tissues. Hence, opioid agonist administration has been successfully implemented in pharmacological strategies against ischemia-reperfusion injury in most major organs.

**Importance of blood vessels**

Vascular injury and microcirculatory disturbances from endothelial dysfunction and neutrophil activation are critical events in the pathophysiology of ischemia-reperfusion (56). Because blood vessels supply nutrients and oxygen to all tissues, pharmacological protection targeted at the vascular level may carry ubiquitous benefits against ischemia-reperfusion injury. Experimentally, morphine has been shown to elicit endothelial preconditioning against anoxia-reoxygenation injury by activation of \( K_{ap} \) channels and nitric oxide signaling (57). Additionally, morphine preconditioning has demonstrated to attenuate the release of L-
selectin and intercellular adhesion molecule-1 (ICAM-1) in an animal model of myocardial ischemia, indicating that opioid protection may also involve an attenuation of the deleterious interactions between neutrophils and endothelium (58). A comparable inhibition of ICAM-1 expression and neutrophil adhesion to endothelium could be obtained using a morphine post-conditioning, that is the administration of morphine after the re-oxygenation injury (59). Interestingly, such benefits of morphine against intra-coronary activation of endothelial cells and neutrophils has been demonstrated in patients with acute myocardial infarction (60). Further experimental studies indicate that the vascular effects of opioids are not limited to the coronary microcirculation (61) and could afford protection against ischemia-reperfusion injury in a wide variety of organs.

LUNGS

Ischemic injury to the lungs is a critical problem during surgery for cardiopulmonary bypass, lung resection and lung transplantation (62). In the worst cases, acute lung injury and acute respiratory distress syndrome ensue, with increased morbidity and mortality. Preliminary reports suggested that natural opioids preserve lungs when retrieved for transplantation (63). Additional investigations with an hypothermic lung preservation model (to simulate the clinical conditions of lung storage during transplantation) showed that the δ-opioid DADLE significantly limits ischemic damages and reduces lung edema, decreases vascular and airway resistances, and improves gas exchanges (64). Recently, selective κ-opioid agonist demonstrated relevant activity against the deleterious response to chronic...
lung hypoxia by an attenuation of hypoxic pulmonary vasoconstriction, pulmonary hypertension and right ventricular hypertrophy in animals, which could lead to future clinical applications (65).

**Kidneys**

Kidney transplantation and cardiovascular interventions on the heart and aorta are frequent causes of renal failure secondary to ischemia-reperfusion injury (66). A potential for opioids to protect the ischemic kidney has emerged from experimental results. During multiorgan preservation experiments in dogs, the intravenous administration of plasma containing the opioid-like HIT protein or of the synthetic DADLE extended the survival time of all tested tissues including the kidneys (67, 68). It is now thought that HIT and DADLE induce a preconditioning-like effect involving K_αβγ channels as effectors (69). In a rabbit model of renal ischemia-reperfusion, morphine inhibited superoxide generation by neutrophils, indicating a potential for reducing the oxidative stress to ischemic kidneys (70). In further studies, a single dose of morphine (5 mg.kg\(^{-1}\)) failed to preserve renal function after ischemia-reperfusion (71) but repeated and increasing administration of the opioid (20-30 mg.kg\(^{-1}\) per day, for 5 days) resulted in a marked ischemic tolerance of animal kidneys (72). In a recent work, although ischemic preconditioning alone had no protective effect against renal ischemia in isoflurane anesthetized rats, the addition of remifentanil resulted in a strong protection, raising the potential for opioid-based anesthetic regimens against renal ischemia (73).

**Intestine**

Reduced intestinal blood flow can occur during cardiopulmonary bypass, abdominal aortic aneurysm surgery or intestinal transplantation. Under these circumstances, pharmacological protection of the ischemic gut would be clinically relevant (74). Recent data implicate the opioidergic pathway in intestinal ischemic preconditioning. Hence, humoral factors generated from the coronary effluent of preconditioned animal hearts showed activation of opioid receptors and K_αβγ channels, and elicited mesenteric ischemic tolerance in a naloxone reversible manner (75). In the rat small intestine, ischemic preconditioning locally released Leu-enkephalin, whose importance was demonstrated by abolition of tissue protection after naloxone administration (76). Noteworthy, the same study demonstrated that animal treatment with morphine (300 µg.kg\(^{-1}\) intravenously) mimicked intestinal ischemic preconditioning and resulted in the attenuation of mucosal injury after sustained ischemia. In isolated rabbit jejunum, activation of the δ-opioid receptor subtype was involved in the adaptation to ischemia. Indeed, a δ-opioid agonist limited the ischemic-induced contractile dysfunction whereas a selective δ-antagonist reversed the protection (77).

**Liver**

Liver ischemia-reperfusion is a challenging phenomenon during transplantation or hepatectomy. It may be responsible for perioperative hepatic dysfunction or failure associated with a risk of poor outcome (78, 79). Therefore, the quest for an effective pharmacological protection of the liver has important clinical stakes. In rats, pre-treatment with the synthetic δ-opioid DADLE 45 min before liver ischemia significantly reduced hepatocyte injury as demonstrated by the reduction in transaminase serum level, attenuation of lipid peroxidation, lesser structural changes, and neutrophil infiltration at reperfusion (80). These results are in line with previous reports indicating that both HIT and DADLE improve the viability of the liver and various other canine organs preserved in an autoperfused multiorgan block preparation (67, 68). More recently, morphine was demonstrated to be protective against hepatocyte anoxia-reoxygenation injury through the activation of a K_αβγ channel- and a nitric oxide-dependent pathway, although this effect seemed independent of opioid receptors (81). In a concordant study, Yang and colleagues (82) used a rat model of liver ischemia-reperfusion to demonstrate that remifentanil could confer hepatocyte preconditioning without opioid receptor activation but through the induction of iNOS and a subsequent decreased ROS production and inflammatory response at reperfusion.

**Brain**

Short periods of cerebral ischemia during carotid endarterectomy, intracranial aneurysm exclusion or aortic repair, even under deep hypothermic circulatory arrest, may result in death or irreversible disability (56). Effective and safe
methods to induce ischemic tolerance in the brain is a matter of active research. Studies on natural hibernation led to remarkable observations that the brain, like other major organs, becomes highly resistant to oxygen and glucose deprivation (83). It is known that such organ tolerance to reduced oxygen availability is dependent on the opioid-like activity of endogenous opioids and opioid receptor activation during neuronal postconditioning (84). Implication of δ-opioid receptors in neuroprotective pathways is supported by the observation of an attenuated glutamate excitotoxicity, reduced hypoxic injury and limited infarct volume consecutive to receptor activation and worsened neuronal damage by receptor blockade during the application of the insult (85-87). Evidence accumulates that opioid exposure induces a neuronal preconditioning and a resistance against subsequent ischemia that is comparable to the one elicited by ischemic preconditioning. In cultured neurons, protection by hypoxic preconditioning against severe hypoxia is dependent on δ-opioid receptor activation through an up-regulation of intracellular survival signals (88). In Purkinje cells, Lim and colleagues (89) described a concentration dependent early preconditioning effect of morphine against ischemic injury through the activation of δ-1 opioid receptors, opening of mitochondrial KATP channels and ROS signaling. In an hippocampal hypoxia/hypoglycemia model, morphine exhibited neuroprotection if a sufficient time-window was provided before exposure to the hypoxic/ hypoglycemic challenge (90). In this study, morphine allowed both an early phase (at 3 hours) and a late phase (at 12 hours) of neuronal preconditioning. Recently, activation of μ-opioid receptors by morphine or δ-1 opioid receptors by the selective agonist Tan 67 induced a delayed neuroprotection (one day after exposure) with limited infarct death in neuronal culture and reduced infarct size in experimental stroke (91). Therefore, it appears that opioid protection can acutely manifest at the time of injury but might importantly extend from hours to days after drug exposure by inducing an early and delayed neuronal preconditioning. Furthermore, the opportunity to initiate neuroprotective intervention after the onset of ischemia would have a high clinical relevance. Such post-insult therapy is now possible with the ischemic post-conditioning, which consists in fragmenting the reperfusion phase with short ischemic episodes (92). Consistant with an endogenous release of opioid peptides and opioid receptor activation during neuronal postconditioning is the inhibition of the protection by naloxone (93). Furthermore, morphine administration shortly before reperfusion (opioid post-conditioning) reproduces the brain protection obtained by an ischemic post-conditioning (93). Comparable benefits against post-anoxic neuronal death have been reported with injection of the partial μ-agonist buprenorphine 45 minutes after an experimental cardiac arrest (94). In a stroke model, administration of a selective κ-opioid receptor agonist provided robust neuroprotection even when given up to 6 hours after the initiation of reperfusion (95).

MULTIPLE-ORGAN ISCHEMIA AND HYPXIA

Global tissue ischemia/ hypoxia is considered as a central feature of the multiple organ dysfunction syndrome that accounts for most surgical post-operative death (96). Development of effective strategies against poor tissue perfusion, hypoxia and organ failures may be of significant benefit in high risk surgical patients (97). It was long recognized that acute adaptation to hypoxia (hypoxic preconditioning) is dependent on endogenous opioids and activation of δ-1 opioid receptors (98). Additionally, administration of morphine or a selective δ-1 opioid agonist has been demonstrated to increase tolerance against lethal hypoxia and improve survival time in animals (99, 100). Recently, systemic administration of selective δ-opioid receptor agonists allowed not only an early (at 20 min) but also a late (at 24 hours) preconditioning protection against hemorrhagic shock-induced global ischemia, with improved hemodynamic stability, plasma lactate levels and overall survival (101, 102). Similarly, selective agonists of the δ2-opioid receptor enhanced cardiac function and facilitated hemodynamic recovery from an hemorrhagic shock (103). In a rat model of hemorrhagic shock, pre-treatment with morphine sulfate (10 µg.kg⁻¹) resulted in an attenuation of leucocyte adherence in the microvessels and microvascular permeability, suggesting opioid protection at the vascular level with reduced shock-induced inflammatory response (104). In an animal model of cardiac arrest followed by resuscitation, pentozone (0,3 mg.kg⁻¹) not only reduced systemic oxygen consumption and lactate production during cardiac arrest but improved myocardial function and animal survival in the post resuscitation period (105). A mechanism akin to preconditioning and mediated by KATP channels is now advanced to explain...
protection of major organs and improved outcome of cardiopulmonary resuscitation by δ-opioid receptor stimulation (106).

**Miscellaneous**

Opioid receptors have a widespread location both in the central nervous system and in the periphery. Opioids modulate the function of a large number of cell subtypes (14). This probably explains the increasing number of works documenting an opioid-induced protective activity in tissues of different origins, including the spinal cord (107), skeletal muscles (108), skin (109), retina (110) and gonads (111). At the light of the current knowledge, it seems that opioid-induced preconditioning and post-conditioning represent an ubiquitous process, applicable in most if not all organs with a considerable potential for clinical applicability.

**Future Directions and Clinical Perspectives**

Synthetic opioids have been used for decades by anesthesiologists to relieve surgical pain. The discovery of opioid-induced preconditioning and post-conditioning may represent new therapeutic opportunities to protect ischemic organs during anesthesia and could change the future of our practice. Preliminary results of human studies indicating an opioid-induced myocardial protection are promising and can no longer be ignored. However, there remain important considerations with the molecules to be selected for this purpose, since all opioids are not equivalent (28) and subtle differences such as stereoselectivity of enantiomers may have importance to elicit organ protection (112). Furthermore, the optimal doses and routes of administration of the drug will have to be evaluated. Interestingly, recent studies have raised perspectives with low doses of opioids through intrathecal injection (i.e. morphine at concentrations comparable to those used for clinical analgesia), which demonstrated a cardioprotective activity in animals (113, 114). In addition, the combination of opioids with volatile anesthetics (115) or other perioperative medications may enhance the beneficial effects of either drug alone. Therefore, future research will have to precise whether certain protocols of opioid administration are susceptible to offer clinically relevant benefits.

**Conclusion**

Abundant experimental researches have demonstrated that opioid receptor agonists offer, beyond analgesic properties, a protective activity against ischemia-reperfusion in a wide variety of tissues. In humans, recent studies brought promises with regard to myocardial protection with opioids. Further clinical trials are now warranted to precise the extent to which opioids may help physicians to preserve the heart and other major organs against ischemic injury. In the future of anesthetic practice, the development of specific opioid-based regimens may have importance for the postoperative recovery and outcome in procedures at risk of ischemic injury.

**References**

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