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Myocardial protection in cardiac surgery: a comprehensive review of current therapies and future cardioprotective strategies

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Cardiac surgery with cardiopulmonary bypass results in global myocardial ischemia–reperfusion injury, leading to significant postoperative morbidity and mortality. Although cardioplegia is the cornerstone of intraoperative cardioprotection, a number of additional strategies have been identified. The concept of preconditioning and postconditioning, despite its limited direct clinical application, provided an essential contribution to the understanding of myocardial injury and organ protection. Therefore, physicians can use different tools to limit perioperative myocardial injury. These include the choice of anesthetic agents, remote ischemic preconditioning, tight glycemic control, optimization of respiratory parameters during the aortic unclamping phase to limit reperfusion injury, appropriate choice of monitoring to optimize hemodynamic parameters and limit perioperative use of catecholamines, and early reintroduction of cardioprotective agents in the postoperative period. Appropriate management before, during, and after cardiopulmonary bypass will help to decrease myocardial damage. This review aimed to highlight the current advancements in cardioprotection and their potential applications during cardiac surgery.

KEYWORDS

cardiac surgery, ischemia–reperfusion injury, myocardial protection, preconditioning, postconditioning

1 Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) includes an expected ischemia–reperfusion (I/R) sequence, leading to myocardial injury and significant postoperative morbidity and mortality. The unavoidable and sustained elevation of postoperative serum troponin is multifactorial because of direct surgical trauma, systemic inflammation, and reversible ischemia or irreversible necrosis. Its short- and long-term prognosis value has been validated for years (1–3). Irrespective of the surgical procedure itself, the early or late elevation of peak serum troponin I has probably a distinct meaning, with a pejorative value in cases of elevation beyond the 24th postoperative hour (4, 5). A large prospective cohort study recently demonstrated that threshold values of hypersensitive troponin I above 5,670 ng/L on postoperative day 1 after coronary artery bypass grafting (CABG) or aortic valve surgery and above 12,981 ng/L following other cardiac surgeries were associated with increased mortality at day 30 (6). A whole literature on myocardial protection techniques during cardiac surgery has therefore emerged. While cardioplegia remains the cornerstone of intraoperative cardioprotection, the lack of consensus

on its practice is striking. The concept of cardioplegia is based on the administration of a hyperkalemic solution that induces a rapid diastolic arrest by depolarizing cardiomyocytes. Different solutions and components (crystalloids, warm or cold blood cardioplegia, anterograde, retrograde, or combined delivery approaches) are used by surgical teams and make synthesis difficult (7). It is beyond the scope of this review to provide a detailed overview of the different cardioplegia solutions and practices. In this update, we will focus on other cardioprotection approaches administered during cardiac surgery that have been developed in addition to cardioplegia techniques.

2 The concept of preconditioning and postconditioning

In 1986, Murry et al. (8) published an experimental study that had a major impact and proved to be a turning point in the field of cardioprotection. Using an *in vivo* animal model, they demonstrated that four brief sequences of 5 min I/R, applied just before a lethal 40-min ischemia, reduced the size of myocardial infarction by more than 75% (Figure 1). The ischemic preconditioning concept was born. Then, we learned that patients presenting with an inaugural myocardial infarction have greater myocardial damage than those whose infarction is preceded by a period of angina (9). Shortly after, Ishihara et al. (10) demonstrated that prodromal angina occurring before the onset of infarction had a beneficial effect on long-term prognosis. The human myocardium is therefore just as receptive as the animal myocardium to the preconditioning signal. It is possible to modify the phenotype of the myocardium before an ischemic process so that it increases its tolerance to oxygen deprivation. By shifting the time-dependent necrosis curve to the right, preconditioning reduces the lesion for a given time.

Myocardial reperfusion, while essential to limit the infarct size, can itself induce injury, thereby reducing its expected beneficial effects (11). It is described as a double-edged sword. Several abrupt metabolic and biochemical changes occur within minutes of reperfusion, including the generation of reactive oxygen species (ROS), intracellular calcium overload, and rapid restoration of normal intracellular pH. In 2003, Zhao et al. (12) demonstrated that the application of brief I/R sequences in the early stages of reperfusion limited myocardial injury. By analogy with the preconditioning phenomenon, this strategy applied following ischemia is known as ischemic postconditioning (Figure 1) and has been described in humans. Indeed, in patients with ongoing acute myocardial infarction, necrosis size has been significantly reduced by 36% using sequential re-inflation of the intracoronary balloon upstream of the stenting zone (13). Moreover, postconditioning by angioplasty has shown better long-term benefits in patients with acute myocardial infarction, including a reduction in infarct size at 6 months and an improvement in myocardial contractile function at 1 year (14).

Abbreviations: CPB, Cardiopulmonary bypass; I/R, Ischemia/reperfusion; CABG, Coronary artery bypass graft; ROS, Radical oxygen species; RIPC, Remote ischemic preconditioning; NO, Nitric oxide; COX-2, Cyclooxygenase-2; K_{ATP}, ATP-gated potassium; RISK, Reperfusion injury salvage kinases; SAFE, Survivor activating factor enhancement; mPTP, Mitochondrial permeability transition pore; VHA, Volatile halogenated agents; eNOS, Endothelial NO synthase; MAC, Minimal alveolar concentration; PI3K, Phosphatidylinositol-3-kinase.

Preconditioning and postconditioning are ubiquitous processes that protect organs against I/R injury. Many organs other than the myocardium (such as the brain, lung, kidney, digestive tract, and skeletal muscle) respond to conditioning. We also know that the various protective signals are transmitted remotely within the body via neuronal and humoral pathways, a process known as remote ischemic preconditioning (RIPC, Figure 2) (15). Finally, preconditioning can protect an organ for up to 24–72 h before an ischemic episode. This phenomenon, known as the late phase of preconditioning, follows the activation of protein neo-syntheses such as nitric oxide (NO) synthases and cyclooxygenase-2 (COX-2) in response to the administration of a signal-inducing protection (16). A vast body of literature has been devoted to deciphering the cellular mechanisms of conditioning (17, 18). Experimental studies carried out on both *in vivo* and *in vitro* models (isolated perfused heart, cell culture preparation, etc.) clarified the more intimate mechanisms (Figure 3). In brief, the protective signal travels to the cellular level, involving various surface receptors (notably those coupled with inhibitory G proteins), leading to the production of diacylglycerol, the activation of different protein kinases (such as protein kinase C), and the opening of various channels, such as ATP-gated potassium channels (K_{ATP}). This information will then trigger different protective cascades via the reperfusion injury salvage kinases (RISK) and survivor activating factor enhancement (SAFE) pathways to lead to intracellular mitochondrial effectors. In the event of I/R, those organelles are the site of membrane permeabilization, known as the mitochondrial permeability transition pore (mPTP) opening (19). Permeabilization induces mitochondrial swelling, which causes them to lose their capacity to produce ATP at the level of the respiratory chain, ultimately dislocating within the cytoplasm and releasing pro-apoptotic substances such as cytochrome C. Conditioning works through several mechanisms: (i) delaying the mPTP opening, in particular through its action on a matrix protein (cyclophilin D); (ii) modifying the ROS production at the level of the mitochondrial respiratory chain (inhibition of complex I); and (iii) acting at the mitochondria-associated membrane, junction zones between the mitochondria, and the sarcoplasmic reticulum (20–23).

3 Volatile halogenated agents-induced myocardial protection

3.1 Experimental approach to myocardial conditioning with volatile halogenated agents

Ischemic conditioning has little direct clinical application in cardiac surgery. Numerous experimental studies have therefore focused on identifying the mechanisms of conditioning to decrypt, mimic, or amplify them. Volatile halogenated agents (VHAs) are the typical pharmacological application of the concept of conditioning in the operating room (Figure 1). Following several studies published in the late 80s, three independent teams demonstrated in 1997 the preconditioning effect of VHA (24–26). Comparing total intravenous anesthesia to VHA on a rabbit model, they reported a significant cardioprotective effect of VHA depending on both adenosine receptors and protein kinase C (24) and found that temporary administration of isoflurane reduced infarct size in dogs (25). The sulfonylurea glyburide abolished VHA-induced cardioprotection, highlighting the role of K_{ATP} channels in this mechanism (25). Since

then, numerous studies have shown that VHA, administered before ischemia, reduced the size of myocardial infarction (27). This protective effect persists for several hours, a phenomenon called VHA-induced late preconditioning or second window of preconditioning (16). Meanwhile, Tanaka et al. (28) showed that animals anesthetized for 120 min with isoflurane had more than a 40%

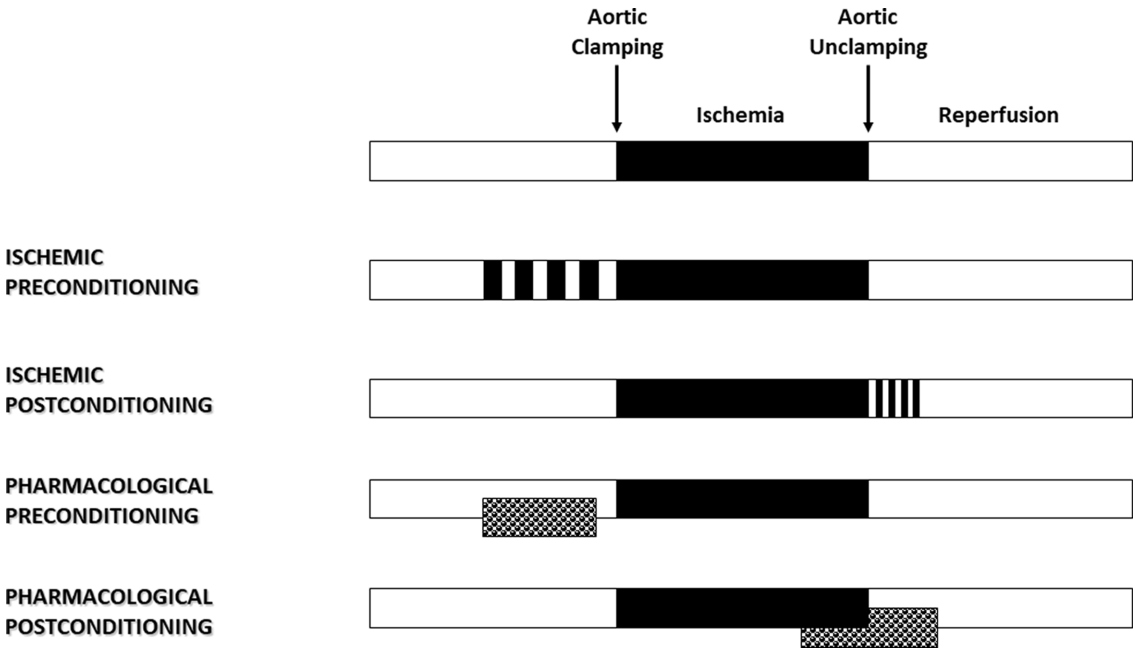

FIGURE 1
Ischemic and pharmacological preconditioning and postconditioning.

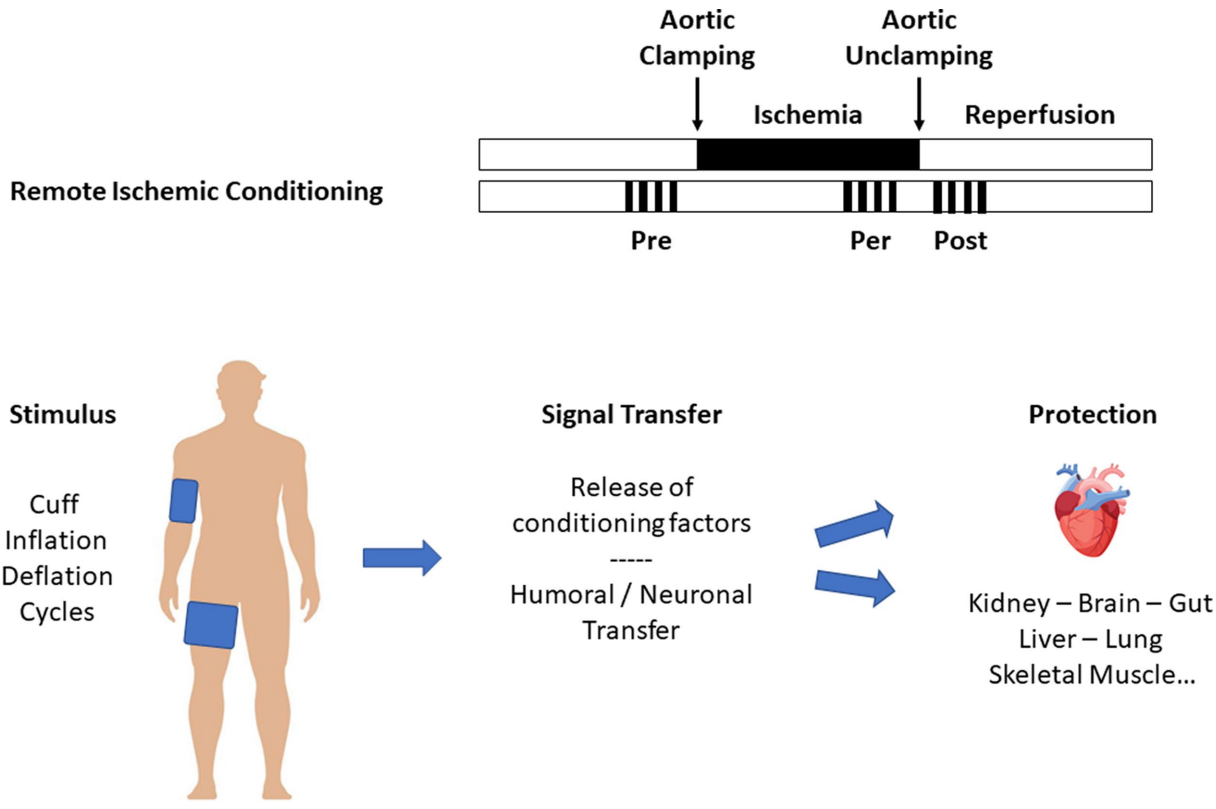

FIGURE 2
Remote ischemic conditioning.

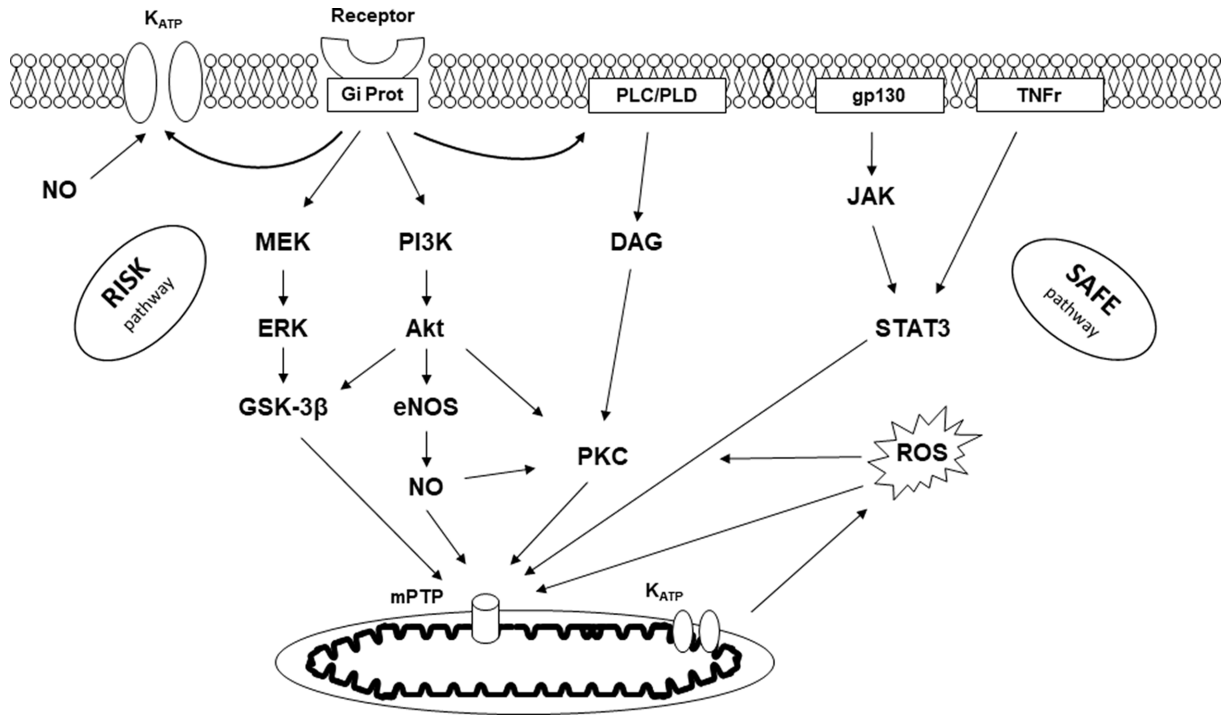

FIGURE 3
Signaling pathway of conditioning. K_{ATP}, ATP-dependent potassium channel; Gi Prot, inhibitory G protein; PLC/PLD, phospholipase C/D; gp130, glycoprotein 130; TNFr, tumor necrosis factor receptor; RISK, reperfusion injury salvage kinase; SAFE, survivor activating factor enhancement; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; GSK-3β, glycogen synthase kinase-3β; PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B; NO, nitric oxide; eNOS, endothelial NO synthase; DAG, diacylglycerol; PKC, protein kinase C; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; ROS, radical oxygen species; mPTP, mitochondrial permeability transition pore.

reduction in myocardial infarct size. This process results from the neosynthesis of proteins such as COX-2 (28) and endothelial NO synthases (eNOS) in response to VHA administration (29). In the late 1990s, several studies demonstrating the postconditioning effect of VHA were published (30–32). On isolated perfused hearts or *in vivo* models, halothane, enflurane, isoflurane, sevoflurane, and desflurane reduced myocardial injury when applied only during reperfusion. Sevoflurane-induced protection was observed at one minimal alveolar concentration (MAC), with no additional benefit at a higher dose (32). Even after cardioplegia, sevoflurane and desflurane provided additional protection when administered at the early phase of reperfusion (33). Intriguingly, 2 min of administration during reperfusion provided maximum protection, whereas less protective effects were observed with longer administration (34). The administration of one MAC isoflurane started 3 min before coronary reperfusion and maintained for only the first 2 min of reperfusion reduced myocardial infarct size by 50%, a phenomenon mediated by the activation of phosphatidylinositol-3-kinase (PI3K) signal transduction (35). VHA administration at this point could have a preferential impact at the mitochondrial level, resulting in a temporary inhibition of respiration, depolarization, and mitochondrial pH, subsequently slowing the opening of mPTP during the first time of reperfusion (36). Thus, VHAs are able to induce both valuable preconditioning and postconditioning (27, 37). Importantly, any postconditioning treatment must be applied at the initial phase of reperfusion before irreversible damage occurs. If the intervention is delayed for even 10 min, the protection is lost (38). In other words, VHA administration must be started a few minutes before reperfusion (before aortic unclamping) and continued immediately afterward in order to have a full protective effect.

3.2 Clinical studies of volatile halogenated agents in cardiac surgery

As early as 1999, Belhomme et al. (39) demonstrated that the administration of 5 min of isoflurane before aortic clamping during CABG surgery induced the activation of protein kinase C (a decisive step in the protective signaling pathway) as well as a decrease in postoperative troponin I. Subsequently, several studies by de Hert et al. (40–42) found marked cardioprotective effects of sevoflurane compared to propofol, responsible for the improvement in postoperative myocardial function, lower postoperative troponin I release, and shorter stay in the intensive care unit and hospital. Sevoflurane (43) and desflurane (44) significantly reduced postoperative troponin release in off-pump CABG surgery. However, those initial encouraging results have not been confirmed by other teams (45–48). More recently, the large MYRIAD trial (49), prospectively including over 5,000 patients in 36 centers, failed to demonstrate a benefit of VHA on 1-year mortality compared to intravenous anesthesia: 2.8% versus 3.0% (RR 0.94 [95% CI: 0.69–1.29], $p = 0.71$).

Several points need to be discussed. Anesthetic preconditioning seems to be more effective following repeated administration spaced

by washout periods than continuous administration before ischemia. Two administrations of sevoflurane at one MAC spaced for at least 10 min significantly reduced serum troponin T release compared to a single continuous administration in patients undergoing CABG (50). Similarly, better cardioprotection following the administration of two sequences of one MAC sevoflurane for 5 min interspersed by a 5-min washout was found when compared with a single administration before CPB (51). The VHA administration protocol during surgery plays certainly a key role in the success of perioperative conditioning. Thus, the administration of VHA throughout surgery, including CPB, provided better protection than administration only before or after CPB (52). This specific efficiency of VHA, when administered during CPB, could be related to their immunomodulatory effects (53, 54). Finally, those cardioprotective effects of VHA must also be linked to their potential beneficial renal effects. It was reported in patients scheduled for CABG surgery that 10 min administration of two MAC sevoflurane during CPB and before aortic clamping significantly decreased postoperative release of brain natriuretic peptide and plasma cystatin C, biochemical markers of myocardial contractile, and renal dysfunction (55). The 1-year follow-up of this last cohort showed a reduced incidence of late cardiac events after surgery (56). Among the many meta-analyses published on the topic, Uhlig et al. (57) reviewed 45 cardiac surgery clinical studies involving 4,840 patients and found a reduction in overall mortality with VHA (OR 0.55; 95% CI: 0.35–0.85), as well as a reduction in perioperative complications. Similar results have been reported when VHAs were used throughout the surgical procedure (OR 0.66 [95% CI: 0.49–0.89]) (58). Those meta-analyses included small and sometimes single-center studies (59). International guidelines are in favor of the use of VHA during cardiac surgery (60, 61).

4 Remote ischemic preconditioning

The heart and other organs can be protected against I/R by applying brief periods of non-lethal I/R sequences to remote tissues, a phenomenon called RIPC (15). The simplest way to perform RIPC is to repeatedly inflate above systolic blood pressure, a blood pressure cuff placed at the root of the upper and/or lower limb (Figure 2). Numerous experimental studies demonstrated that the protective signal was transmitted to other organs, including the heart, via humoral and neuronal pathways. In a proof-to-concept study, Hausenloy et al. (62) demonstrated that a RIPC protocol consisting of three 5-min cycles of upper limb ischemia significantly reduced the postoperative troponin T release in patients undergoing CABG surgery. Other studies subsequently confirmed these initial encouraging results (63, 64). Meanwhile, Zarbock et al. (65) investigated the benefit of RIPC on renal protection during CPB and found that RIPC reduced acute kidney injury by 15% in high-risk patients. In a follow-up study of the same cohort, they showed persistent renal protection at 90 days with an 18% absolute risk reduction of acute kidney injury (66). However, those promising results have not been confirmed by others. A cycle of 3 × 5-min cuff inflations to 200 mmHg separated by 5-min periods of cuff deflation did not reduce troponin release or other organ protection during cardiac surgery (67). More recently, two multicenter, prospective, randomized trials involving a large number of patients were unable to demonstrate any benefit of RIPC. The RIPHeart study (68) found that a RIPC protocol did not modify the rate of a composite endpoint (postoperative myocardial infarction, stroke, renal failure, and death within 90 days) in 1,385 patients undergoing cardiac surgery. Similarly, the ERICCA trial (69) included 1,612 patients and, using a similar design and endpoint, found no benefit of RIPC. Moreover, a protocol combining RIPC and postconditioning (four cycles of 5-min ischemia/5-min reperfusion applied before and after CPB) did not improve the outcome in 1,280 patients scheduled for cardiac surgery (70). Finally, meta-analyses confirmed that RIPC could reduce postoperative troponin release without clinical benefit to overall outcomes (71, 72).

Several factors are expected to interfere with the clinical effectiveness of RIPC. The algorithm is probably of major importance in terms of the number of cycles, the duration of each ischemic sequence, and the RIPC application site (arm and/or thigh) (73, 74). In an *ex vivo* mice Langendorff model, Johnsen et al. (73) found that four, six, or eight cycles were effective, while two were not. Ischemic cycles lasting 2 min or 5 min reduced infarct size, but 10 min abolished cardioprotection. In clinical studies, the majority of medical staff use a 5-min ischemia protocol. There may be a dose dependence on the RIPC protocol, as previously suggested (74). Increasing the power of the stimulus could also be more effective, as demonstrated in patients undergoing cardiac surgery and having received a RIPC protocol by simultaneous inflation of a balloon on both the arm and the thigh (75). Drugs administered during cardiac surgery may also interfere with the effectiveness of a RIPC protocol. Thus, nitrates (despite their intrinsic cardioprotective properties) can inhibit the beneficial effect of RIPC (75, 76). Nitrates could inhibit RIPC-induced cardioprotection by NO inhibiting afferent nerve conduction in the limb. In the ERIC-GTN study (76), intravenous infusion of nitrates during surgery abrogated RIPC protection. Anesthetic agents could also affect the cardioprotective effectiveness of RIPC. Kottenberg et al. (77) reported that RIPC reduced the postoperative troponin release after CABG surgery in patients receiving isoflurane but not propofol. This latest study can be interpreted in two ways. Either the RIPC protocol was insufficiently powerful to protect the myocardium under clinical conditions and required synergistic protection by isoflurane or propofol by itself negated the protective effect of RIPC. Indeed, experimental studies have shown that propofol abolishes desflurane-induced preconditioning and RIPC (78, 79). In a recent meta-analysis focusing on the renal protective effects of RIPC, the authors emphasized that RIPC's beneficial effects were mainly found during anesthesia with VHA (80).

5 Glycemic balance

Hyperglycemia is both a common phenomenon observed during cardiac surgery and a well-known independent risk factor of mortality (81, 82). In a large cohort including more than 8,000 patients undergoing cardiac surgery, Ascione et al. (83) found that 15% of them had blood sugar levels above 200 mg/dL, more than half of perioperative hyperglycemia occurring in non-diabetic patients. Hyperglycemia was associated with postoperative myocardial infarction (OR: 2.73 [95% CI, 1.74–4.26]). Among various processes, acute hyperglycemia increases ROS production, leading to endothelial dysfunction and worsening of myocardial I/R injury (84–86). Experimentally, myocardial infarct size was linearly related to blood glucose concentration (87). Several studies have also demonstrated that cardioprotective strategies such as VHA-induced preconditioning and postconditioning were abolished in

hyperglycemic conditions (88–90). In addition, oral antidiabetic drugs such as glyburide could also inhibit preconditioning (25). Insulin is therefore a first-line therapy during cardiac surgery. In addition to lowering blood glucose levels, insulin has cardioprotective properties by activating the RISK pathway, especially when administered during reperfusion (91–93). It is important to emphasize the benefit of continuous infusion of insulin rather than boluses (94, 95). Beyond hyperglycemia, the variability of blood glucose concentration is harmful (96). If hyperglycemia must be undoubtedly treated (97), the current objective is to determine the optimal blood glucose threshold to be reached during cardiac surgery. Several studies reported an increased incidence of stroke (98) and delirium (99) during intraoperative tight glucose control. In a retrospective study of 4,000 patients treated at the Cleveland Clinic, Duncan et al. (100) reported that maintaining intraoperative blood glucose levels below 140 mg/dL increased morbidity and mortality. However, the same team conducted a prospective study in which a treated group received a fixed high-dose insulin and concomitant variable glucose infusion during cardiac surgery (101). In more than 1,400 randomized patients, they observed a 38% reduction of 30-day morbimortality in the treated group, demonstrating once again the intraoperative protective effect of insulin. The current consensus is, therefore, to treat with continuous insulin infusion when intraoperative blood glucose values are 180 mg/dL (10 mM) or higher; the target range is between 140 and 180 mg/dL (7.7–10 mM) (102–106). Finally, glycemic management appears to be an integral part of the cardioprotection strategy during cardiac surgery (Figure 4).

6 The challenge of aortic unclamping

6.1 Oxygenation control

Uncoupling of the mitochondrial respiratory chain during ischemia induces ROS overproduction in the event of excessive oxygenation at reperfusion (107). *In vitro* and *in vivo* experiments demonstrated that hyperoxic reperfusion increased inflammatory response and apoptosis and altered hemodynamic performances (108). Additionally, hyperoxia causes a significant reduction in coronary blood flow, which can further exacerbate reperfusion injury (109). Several clinical studies emphasized the potentially harmful effects of high-concentration oxygen therapy for the treatment of heart disorders in the medical setting (110, 111). The AVOID trial (112) showed, in non-hypoxemic patients suffering from ST-segment elevation myocardial infarction, that high-flow O_2 therapy at reperfusion increased the peak of creatine kinase and the rate of recurrent myocardial infarction. Similarly, a recent meta-analysis (113) did not find evidence to support the use of oxygen therapy in normoxemic patients with acute myocardial infarction. Although debated, those questions arise in the context of cardiac surgery with CPB (114–116). In pediatric heart surgery, controlled reoxygenation during CPB decreased the markers of inflammation and organ damage (117). In patients scheduled for CABG surgery, hyperoxia ($PaO_2 = 400$ mmHg) compared to normoxia ($PaO_2 = 140$ mmHg) during CPB increased oxidative myocardial damage (118). Inoue et al. (119) explored the effects of reducing hyperoxia ($PaO_2 = 450–550$ mmHg versus 200–250 mmHg) during reperfusion in cardiac surgery. They found that lowering the reperfused PaO_2 after aortic unclamping significantly reduced oxidative damage and myocardial enzyme release. Conversely, McGuinness et al. (120) failed to demonstrate any difference in myocardial ischemia damage when comparing modest hyperoxia (178 mmHg) with normoxia. Interestingly, there was significant pre- and post-CPB hyperoxia (approximately 200 mmHg) in both groups, precisely during high-risk periods of hyperoxia-induced cellular damage. It is therefore quite likely that hyperoxia at the time of aortic unclamping may worsen myocardial lesions. Moreover, intraoperative oxidative damage is associated with postoperative delirium and neuronal injury (121). To sum up, it

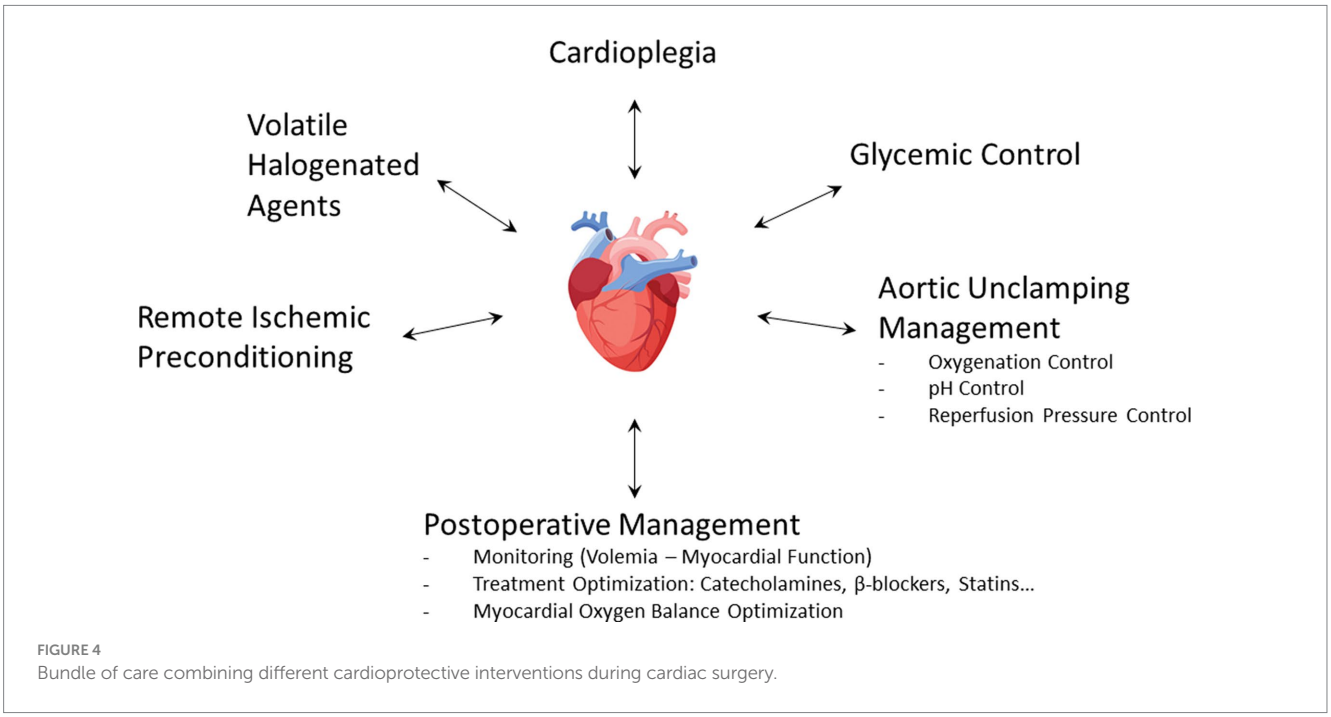

FIGURE 4
Bundle of care combining different cardioprotective interventions during cardiac surgery.

seems reasonable to advise that excessive use of supplemental oxygen in normoxic patients, particularly at the time of aortic unclamping, could potentially lead to exacerbated myocardial injury (Figure 4).

6.2 Impact of acid–base balance

Using a pH electrode on a rabbit heart model, Cobbe et al. (122) demonstrated that tissue pH fell continuously during ischemia because of progressive H^+ ion accumulation, with a rapid recovery of pH during the first minutes of reperfusion. However, it has been shown that part of reperfusion injury comes from the rapidity of the pH rise. In rat livers, a slow increase in pH over 15 min after reperfusion dramatically reduced LDH release, a phenomenon known as pH paradox (123). Some years later, this result was confirmed on a cardiomyocyte model (124). It is well established that sudden reperfusion generates ROS production and induces calcium overload (125). Rapid recovery of cellular acidosis during the first moment of reperfusion ultimately leads to hypercontraction of the myocardium. At this point, ROS production at the mitochondrial level induces mPTP opening and subsequent myocyte death, a phenomenon that can be prevented by initial acidotic reperfusion (126). Several techniques, such as hypercapnic acidosis and Na^+/H^+ exchange inhibition, used during reperfusion attenuate lethal damage, whereas an alkaline solution (pH = 7.6) aggravated it (127). How long this temporary acidosis should be maintained after reperfusion is probably a pivotal question. Using a Langendorff-isolated rat heart model, Ohashi et al. (128) found that reperfusion for less than 3 min with an acid solution provided better recovery. Experimentally, acid reperfusion for 3 min delays the normalization of myocardial tissue pH and enhances myocardial salvage (129). Several studies suggest that the protective effect of postconditioning could be mediated by prolonged transient acidosis (130–133). Experimentally, infusion of NaHCO3 during a postconditioning protocol abolished cardioprotection and blunted the activation of RISK pathways (130). It is postulated that postconditioning prevents mPTP opening by maintaining temporary acidosis during the first minutes of reperfusion (131). VHA could also induce postconditioning through inhibition of respiration, depolarization, and ultimately mitochondrial acidification upon reperfusion (36). A complementary approach to maintaining a temporary acidosis during reperfusion is to inhibit Na^+/H^+ exchange. Administration of cariporide reduced Na^+ overload and contributed to H^+ extrusion during reperfusion (134, 135). Interestingly, this process also leads to a drop in Ca^{++} level during reperfusion (136). This proof of concept was demonstrated in the prospective, multicenter EXPEDITION study (137), which included 5,761 patients undergoing high-risk CABG surgery. The administration of cariporide before, during, and after surgery significantly reduced the incidence of myocardial infarction from 18.9% in the placebo group to 14.4% in the treatment group. However, because of an increase in cerebrovascular events in the treated group, the clinical use of cariporide was halted. Surprisingly, the EXPEDITION study design required cariporide administration to be continued for 48 h after surgery, i.e., a potentially too long way from the time of myocardial reperfusion. To summarize, the myocardial tissue is subject to significant pH variations at the time of aortic unclamping. At the very least, the clinician should avoid any alkalosis just before and just after myocardial reperfusion, which is very likely to be deleterious at this stage (Figure 4).

6.3 Controlling reperfusion pressure

Reperfusion injury may also be the result of excess pressure in the first moments following aortic unclamping. Okamoto et al. (138) demonstrated that early gentle reperfusion (50 mmHg versus 80 mmHg during the first 20 min of reperfusion) limited the post-ischemic damage in animals subjected to 4 h of ischemia. Similarly, a staged reperfusion protocol in which the coronary perfusion pressure was maintained at 40% of control for 0–3 min after the onset of reperfusion, 60% of control for 4–6 min, and 80% of control for 7–10 min has been suggested (139). This graduated reperfusion could mitigate myocardial stunning via transient acidosis during early reperfusion. Controlled reperfusion decreases calcium deposition and increases both mitochondrial oxidative phosphorylation rate and myocardial ATP content (140). Furthermore, low-pressure reperfusion limited myocardial necrosis by inhibiting mPTP opening on an isolated Langendorff heart model (141). Low-pressure reperfusion appears to offer similar protection to that provided by postconditioning, both techniques involving the activation of the PI3K-mPTP pathway (142). Testing this concept of gradual reperfusion on a population of patients undergoing CABG surgery, other authors (143) found a significant regression of interstitial edema at 60 min reperfusion. Although it is well established that excessive pressure worsens myocardial damage during reperfusion, there is currently no precise scheme for gentle reperfusion that can be clinically applied. Consequently, the practical implementation of this concept varies widely from one center to another (144).

7 The postoperative period

During the postoperative period, several factors will also influence myocardial tolerance to cardiac surgery with CPB. Maintaining the right balance between myocardial oxygen supply and demand remains a key issue. A transfusion threshold adapted to the needs of the myocardium and resumption of treatments such as beta-blockers at an early stage is traditionally part of good practices. In addition, two other specific points are worth mentioning here. During cardiac surgery, catecholamines are widely used to prevent or treat low-cardiac output syndrome, depending on preoperative patients' status, the complexity of the surgical procedure, and, above all, the physician's decision (145, 146). However, those drugs should be used only as needed to maintain adequate organ perfusion (147). Because of their positive inotropic and/or chronotropic effects, the overuse of catecholamines can lead to cardiac arrhythmias and myocyte death. Studying a large cohort of patients undergoing conventional cardiac surgery, we found (148) that perioperative use of dobutamine, simply based on the clinical judgment of the anesthesiologist, increased postoperative major cardiac morbidity. Exploring the data of a national cohort of 6,005 consecutive cardiac surgery patients, Nielsen et al. (149) demonstrated that inotropic therapy was independently associated with short- and long-term postoperative myocardial infarction and death. It seems essential to carefully monitor the patients' macrohemodynamic parameters to correctly assess volemia

and cardiovascular function so that catecholamines can be judiciously used and discontinued as soon as possible. In addition, the pleiotropic beneficial effects of statins have been widely described, hence their widespread use in cardiac surgery patients (150, 151). Although the administration of statins in the preoperative phase of cardiac surgery has recently been shown to be ineffective, physicians must be aware that these drugs can cause a rebound effect (152–154). Postoperative statin withdrawal was an independent predictor of postoperative myocardial infarction after major vascular surgery (155). Initiation of statin treatment results in endothelial eNOS upregulation due to the inactivation of a Rho protein, which usually inhibits eNOS. In the case of statin chronic therapy discontinuation, there is an overshoot translocation and activation of Rho, causing downregulation of eNOS production below baseline levels (156).

TABLE 1 Positive and negative clinical modulators of myocardial protection by conditioning.

Factors inducing cardioprotection	Factors inhibiting cardioprotection
Volatile halogenated agents	Hyperglycemia
Insulin	Diabetes
Estrogens	Aging
Opioids	Sulfonylureas
Xenon	Hyperoxia
Cyclosporin A	Alkalosis
Nitric oxide	Nitrates
Statins	
Lidocaine	

8 Modulating factors

During the intraoperative period, due to the multiplicity of patient-related factors (comorbidities and treatments) as well as operative techniques (anesthetic agents, CPB, and cardioplegia), the efficacy of cardioprotective techniques is questionable. First, the phenomenon of cardiac conditioning is influenced by age, with drop-in effectiveness in elderly patients (157). Senescent myocardium is particularly sensitive to ischemia, probably due to metabolic degradation and impaired mitochondrial function (158, 159). A progressive loss of response to preconditioning was demonstrated by comparing three cohorts of 3-, 12-, and 20-month-old rats subjected to 1 or 3 cycles of ischemic preconditioning (160). It has also been shown that the protective effect of sevoflurane gradually disappeared with age (161). Second, the cardioprotective effects of estrogens and their possible interference with preconditioning have been regularly reported. Estrogens are thought to be protective via several mechanisms: activation of K_{ATP} channels, reduced leukocyte adhesion, ROS, and NO production, and reduced calcium influx during ischemia (162–166). In an experimental study, the injection of 17b-estradiol was shown to induce cardioprotection mediated by mitochondrial K_{ATP} channels, identical to that of ischemic preconditioning (162). It was also found under similar conditions that female mice were already protected and that ischemic preconditioning did not provide any additional protection (167). Myocardial infarct size was significantly smaller in female rabbits compared to male rabbits, and isoflurane did not provide any additional benefit (166). Third, many pharmacological agents used during surgery could interfere with perioperative cardioprotection (Table 1). Several reviews have focused on the cardioprotective effects of opioids (168–170). These agents act via activation of κ-, δ-, and/or even μ-opioid receptors, leading to protein kinase C activation and potentiation of K_{ATP} channels opening (171, 172). Propofol is known to abolish myocardial conditioning, possibly due to its ROS scavenger effects (79, 173). Ketamine inhibits ischemic preconditioning through its action on K_{ATP} channels (174). This pharmacological effect appears to be linked to the stereoselectivity of ketamine since the S(+)-form is neutral on both early and late preconditioning (175, 176). Lidocaine could also interfere with either anti-apoptotic cardioprotective or antagonist effects (177–179). A large prospective, comparative, randomized, multicenter study demonstrated that xenon, known to induce preconditioning and postconditioning (180, 181), significantly reduced postoperative troponin release in patients undergoing CABG surgery when compared to total intravenous anesthesia (182). Cyclosporine, in addition to its immunosuppressive properties, is a potent inhibitor of mPTP opening by preventing the calcium-induced interaction of cyclophilin D with a pore component (183). A single intravenous bolus of cyclosporine administered before CPB—as preconditioning (184)—or 10 min before aortic cross-unclamping—as postconditioning (185)—reduced the extent of myocardial injury in patients undergoing CABG or aortic valve surgery. However, clinical trials about the use of cyclosporine in cardiac surgery were interrupted following the publication of the large-scale multicenter CIRCUS study (186), which failed to demonstrate any improvement in patients with ST-segment elevation myocardial infarction.

9 Synergistic approaches

Experimental studies have suggested that a bundle of care could reinforce myocardial conditioning (187, 188). The interaction between several interventions to mitigate cardiac reperfusion injury has been shown between VHA and a postconditioning intervention (35). These results further suggest that the administration of 0.5 MAC isoflurane at reperfusion, a concentration that does not provide cardioprotection alone, reduces the threshold of ischemic postconditioning. Huhn et al. (89) showed that hyperglycemia abolished sevoflurane-induced postconditioning and that cyclosporine A reversed this loss of protection. The combination of RIPC with local ischemic postconditioning has previously been tested in ST-elevation myocardial infarction (189, 190). However, the efficacy of those multimodal interventions on surrogate markers of reperfusion injury, such as serum creatine kinase-MB isoenzyme for the RIPOST-MI study (189) or the salvage index by cardiac magnetic resonance imaging for the LIPSIA CONDITIONING study (190), is controversial. The ProCCard study (191) evaluated the relevance of a cardioprotective bundle of care during cardiac surgery with CPB. A total of 210 patients were randomized into a standard-of-care group and a treatment group simultaneously combining five modes of cardioprotection: sevoflurane administration, RIPC, tight intraoperative blood glucose control, induction of a moderate respiratory acidosis to prevent the pH paradox phenomenon, and

gentle reperfusion to limit myocardial reperfusion injury (Figure 4). Unfortunately, the primary endpoint (the postoperative 72-h area under the curve of high-sensitivity cardiac troponin I) was not significantly modified: the mean ratio between control and treatment groups was 0.92; 95%CI: 0.71–1.21; $p = 0.55$. However, VHA administration modalities during CPB could be a crucial point in that study (192). These various factors indicate that the notion of synergy in cardioprotection remains a point that needs to be further explored.

10 Conclusion

After many years of translational research in the field of perioperative cardioprotection with inconsistent results, many questions remain. The specificity of the pathophysiology of I/R during cardiac surgery with CPB makes the equation complex. Notably, the myocardium is subjected to global ischemia on a non-beating heart, to which are added the effects of cardioplegia as well as those of CPB. This review highlighted different perioperative strategies to limit perioperative myocardial injury in patients undergoing cardiac surgery with CPB. Myocardial preconditioning and postconditioning, despite their limited clinical applications, have highlighted the understanding of the underlying mechanisms of intraoperative I/R myocardial injury. It is now up to the healthcare providers to integrate these different elements and maintain a comprehensive approach pre-, intra-, and post-CPB to limit intraoperative myocardial injury as effectively as possible during cardiac surgery.

Author contributions

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References

1. Fellahi JL, Gue X, Richomme X, Monier E, Guillou L, Riou B. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. *Anesthesiology*. (2003) 99:270–4. doi: 10.1097/00000542-200308000-00007

2. Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation*. (2006) 114:1468–75. doi: 10.1161/CIRCULATIONAHA.105.602370

3. Lurati Buse GA, Koller MT, Grapow M, Bolliger D, Seeberger M, Filipovic M. The prognostic value of troponin release after adult cardiac surgery - a meta-analysis. *Eur J Cardiothorac Surg*. (2010) 37:399–406. doi: 10.1016/j.ejcts.2009.05.054

4. Carrier M, Pellerin M, Perrault LP, Solymoss BC, Pelletier LC. Troponin levels in patients with myocardial infarction after coronary artery bypass grafting. *Ann Thorac Surg*. (2000) 69:435–40. doi: 10.1016/s0003-4975(99)01294-1

5. Fellahi J-L, Hanouz J-L, Gué X, Monier E, Guillou L, Riou B. Kinetic analysis of cardiac troponin I release is no more accurate than a single 24-h measurement in predicting in-hospital outcome after cardiac surgery. *Eur J Anaesthesiol*. (2008) 25:490–7. doi: 10.1017/S0265021508003827

6. Devereaux PJ, Lamy A, Chan MTV, Allard RV, Lomivorotov VV, Landoni G, et al. VISION cardiac surgery Investigators. High-sensitivity troponin I after cardiac surgery and 30-day mortality. *N Engl J Med*. (2022) 386:827–36. doi: 10.1056/NEJMoa2000803

7. Chambers DJ, Fallouh HB. Cardioplegia and cardiac surgery: pharmacological arrest and cardioprotection during global ischemia and reperfusion. *Pharmacol Ther*. (2010) 127:41–52. doi: 10.1016/j.pharmthera.2010.04.001

8. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. (1986) 74:1124–36. doi: 10.1161/01.cir.74.5.1124

9. Ottani F, Galvani M, Ferrini D, Sorbello F, Limonetti P, Pantoli D, et al. Prodromal angina limits infarct size. A role for ischemic preconditioning. *Circulation*. (1995) 91:291–7. doi: 10.1161/01.cir.91.2.291

10. Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, et al. Implications of prodromal angina pectoris in anterior wall acute myocardial infarction: acute angiographic findings and long-term prognosis. *J Am Coll Cardiol*. (1997) 30:970–5. doi: 10.1016/s0735-1097(97)00238-6

11. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. (2007) 357:1121–35. doi: 10.1056/NEJMra071667

12. Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. *Am J Physiol Heart Circ Physiol*. (2003) 285:H579–88. doi: 10.1152/ajpheart.01064.2002

13. Staat P, Rioufol G, Piot C, Cottin Y, Cung TT, L'Huillier I, et al. Postconditioning the human heart. *Circulation*. (2005) 112:2143–8. doi: 10.1161/CIRCULATIONAHA.105.558122

14. Thibault H, Piot C, Staat P, Bontemps L, Sportouch C, Rioufol G, et al. Long-term benefit of postconditioning. *Circulation*. (2008) 117:1037–44. doi: 10.1161/CIRCULATIONAHA.107.729780

15. Heusch G, Botker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. *J Am Coll Cardiol*. (2015) 65:177–95. doi: 10.1016/j.jacc.2014.10.031

16. Bolli R, Li QH, Tang XL, Guo Y, Xuan YT, Rokosh G, et al. The late phase of preconditioning and its natural clinical application--gene therapy. *Heart Fail Rev*. (2007) 12:189–99. doi: 10.1007/s10741-007-9031-4

17. Cohen MV, Downey JM. Signalling pathways and mechanisms of protection in pre- and postconditioning: historical perspective and lessons for the future. *Br J Pharmacol*. (2015) 172:1913–32. doi: 10.1111/bph.12903

18. Torregroza C, Raupach A, Feige K, Weber NC, Hollmann MW, Huhn R. Perioperative Cardioprotection: general mechanisms and pharmacological approaches. *Anesth Analg*. (2020) 131:1765–80. doi: 10.1213/ANE.0000000000005243

19. Ong SB, Dongworth RK, Cabrera-Fuentes HA, Hausenloy DJ. Role of the MPTP in conditioning the heart - translatability and mechanism. *Br J Pharmacol*. (2015) 172:2074–84. doi: 10.1111/bph.13013

20. Li B, Chauvin C, De Paulis D, De Oliveira F, Gharib A, Vial G, et al. Inhibition of complex I regulates the mitochondrial permeability transition through a phosphate-sensitive inhibitory site masked by cyclophilin D. *Biochim Biophys Acta*. (2012) 1817:1628–34. doi: 10.1016/j.bbabio.2012.05.011

21. Teixeira G, Abrial M, Portier K, Chiari P, Couture-Lepetit E, Tourneur Y, et al. Synergistic protective effect of cyclosporin a and rotenone against hypoxia-

reoxygenation in cardiomyocytes. *J Mol Cell Cardiol*. (2013) 56:55–62. doi: 10.1016/j.yjmcc.2012.11.023

22. Giorgi C, De Stefani D, Bononi A, Rizzuto R, Pinton P. Structural and functional link between the mitochondrial network and the endoplasmic reticulum. *Int J Biochem Cell Biol*. (2009) 41:1817–27. doi: 10.1016/j.biocel.2009.04.010

23. Paillard M, Tubbs E, Thiebaut PA, Gomez L, Fauconnier J, Da Silva CC, et al. Depressing mitochondria-reticulum interactions protects cardiomyocytes from lethal hypoxia-reoxygenation injury. *Circulation*. (2013) 128:1555–65. doi: 10.1161/CIRCULATIONAHA.113.001225

24. Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anesthetics protect the ischemic rabbit myocardium from infarction. *Anesthesiology*. (1997) 86:699–709. doi: 10.1097/00000542-199703000-00023

25. Kersten JR, Schmeling TJ, Pagel PS, Gross GJ, Warltier DC. Isoflurane mimics ischemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase. *Anesthesiology*. (1997) 87:361–70. doi: 10.1097/00000542-199708000-00024

26. Cason BA, Gamperl AK, Slocum RE, Hickey RF. Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology*. (1997) 87:1182–90. doi: 10.1097/00000542-199711000-00023

27. Pagel PS, Crystal GJ. The discovery of myocardial preconditioning using volatile anesthetics: a history and contemporary clinical perspective. *J Cardiothorac Vasc Anesth*. (2018) 32:1112–34. doi: 10.1053/j.jvca.2017.12.029

28. Tanaka K, Ludwig LM, Krolikowski JG, Alcindor D, Pratt PF, Kersten JR, et al. Isoflurane produces delayed preconditioning against myocardial ischemia and reperfusion injury: role of cyclooxygenase-2. *Anesthesiology*. (2004) 100:525–31. doi: 10.1097/00000542-200403000-00010

29. Chiari PC, Bienengraeber MW, Weihrauch D, Krolikowski JG, Kersten JR, Warltier DC, et al. Role of endothelial nitric oxide synthase as a trigger and mediator of isoflurane-induced delayed preconditioning in rabbit myocardium. *Anesthesiology*. (2005) 103:74–83. doi: 10.1097/00000542-200507000-00014

30. Schlack W, Preckel B, Stunneck D, Thämer V. Effects of halothane, enflurane, isoflurane, sevoflurane and desflurane on myocardial reperfusion injury in the isolated rat heart. *Br J Anaesth*. (1998) 81:913–9. doi: 10.1093/bja/81.6.913

31. Preckel B, Schlack W, Comfère T, Obal D, Barthel H, Thämer V. Effects of enflurane, isoflurane, sevoflurane and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart in vivo. *Br J Anaesth*. (1998) 81:905–12. doi: 10.1093/bja/81.6.905

32. Obal D, Preckel B, Scharbatke H, Müllenheim J, Höterkes F, Thämer V, et al. One MAC of sevoflurane provides protection against reperfusion injury in the rat heart in vivo. *Br J Anaesth*. (2001) 87:905–11. doi: 10.1093/bja/87.6.905

33. Preckel B, Thämer V, Schlack W. Beneficial effects of sevoflurane and desflurane against myocardial reperfusion injury after cardioplegic arrest. *Can J Anaesth*. (1999) 46:1076–81. doi: 10.1007/BF03013206

34. Obal D, Scharbatke H, Barthel H, Preckel B, Müllenheim J, Schlack W. Cardioprotection against reperfusion injury is maximal with only two minutes of sevoflurane administration in rats. *Can J Anaesth*. (2003) 50:940–5. doi: 10.1007/BF03018744

35. Chiari PC, Bienengraeber MW, Pagel PS, Krolikowski JG, Kersten JR, Warltier DC. Isoflurane protects against myocardial infarction during early reperfusion by activation of phosphatidylinositol-3-kinase signal transduction: evidence for anesthetic-induced postconditioning in rabbits. *Anesthesiology*. (2005) 102:102–9. doi: 10.1097/00000542-200501000-00018

36. Pravdic D, Mio Y, Sedlic F, Pratt PF, Warltier DC, Bosnjak ZJ, et al. Isoflurane protects cardiomyocytes and mitochondria by immediate and cytosol-independent action at reperfusion. *Br J Pharmacol*. (2010) 160:220–32. doi: 10.1111/j.1476-5381.2010.00698.x

37. Lemoine S, Tritapepe L, Hanouz JL, Puddu PE. The mechanisms of cardio-protective effects of desflurane and sevoflurane at the time of reperfusion: anaesthetic post-conditioning potentially translatable to humans? *Br J Anaesth*. (2016) 116:456–75. doi: 10.1093/bja/aev451

38. Yang XM, Proctor JB, Cui L, Krieg T, Downey JM, Cohen MV. Multiple, brief coronary occlusions during early reperfusion protect rabbit hearts by targeting cell signaling pathways. *J Am Coll Cardiol*. (2004) 44:1103–10. doi: 10.1016/j.jacc.2004.05.060

39. Belhomme D, Peynet J, Louzy M, Launay JM, Kitakaze M, Menasché P. Evidence for preconditioning by isoflurane in coronary artery bypass graft surgery. *Circulation*. (1999) 100:II340–4. doi: 10.1161/circ.100.suppl_2.Ii-340

40. De Hert SG, ten Broecke PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. *Anesthesiology*. (2002) 97:42–9. doi: 10.1097/00000542-200207000-00007

41. De Hert SG, Cromheecke S, ten Broecke PW, Mertens E, De Blier IG, Stockman BA, et al. Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. *Anesthesiology*. (2003) 99:314–23. doi: 10.1097/00000542-200308000-00013

42. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, ten Broecke PW, De Blier IG, et al. Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. *Anesthesiology*. (2004) 101:9–20. doi: 10.1097/00000542-200407000-00005

43. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *Anesthesiology*. (2003) 99:826–33. doi: 10.1097/00000542-200310000-00013

44. Guarracino F, Landoni G, Tritapepe L, Pompei F, Leoni A, Aletti G, et al. Myocardial damage prevented by volatile anesthetics: a multicenter randomized controlled study. *J Cardiothorac Vasc Anesth*. (2006) 20:477–83. doi: 10.1053/j.jvca.2006.05.012

45. Fellahi JL, Gue X, Philippe E, Riou B, Gerard JL. Isoflurane may not influence postoperative cardiac troponin I release and clinical outcome in adult cardiac surgery. *Eur J Anaesthesiol*. (2004) 21:688–93. doi: 10.1017/s0265021504009044

46. Piriou V, Mantz J, Goldfarb G, Kitakaze M, Chiari P, Paquin S, et al. Sevoflurane preconditioning at 1 MAC only provides limited protection in patients undergoing coronary artery bypass surgery: a randomized bi-Centre trial. *Br J Anaesth*. (2007) 99:624–31. doi: 10.1093/bja/aem264

47. De Hert SG, Vlasselaers D, Barbe R, Ory JP, Dekegel D, Donnadonni R, et al. A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. *Anaesthesia*. (2009) 64:953–60. doi: 10.1111/j.1365-2044.2009.06008.x

48. Flier S, Post J, Concepcion AN, Kappen TH, Kalkman CJ, Buhre WF. Influence of propofol-opioid vs isoflurane-opioid anaesthesia on postoperative troponin release in patients undergoing coronary artery bypass grafting. *Br J Anaesth*. (2010) 105:122–30. doi: 10.1093/bja/aeq111

49. Landoni G, Lomivorotov VV, Nigro Neto C, Monaco F, Pasyuga VV, Bradic N, et al. Volatile anesthetics versus Total intravenous anesthesia for cardiac surgery. *N Engl J Med*. (2019) 380:1214–25. doi: 10.1056/NEJMoa1816476

50. Bein B, Renner J, Caliebe D, Hanss R, Bauer M, Fraund S, et al. The effects of interrupted or continuous administration of sevoflurane on preconditioning before cardio-pulmonary bypass in coronary artery surgery: comparison with continuous propofol. *Anaesthesia*. (2008) 63:1046–55. doi: 10.1111/j.1365-2044.2008.05563.x

51. Frässdorf J, Borowski A, Ebel D, Feindt P, Hermes M, Meemann T, et al. Impact of preconditioning protocol on anesthetic-induced cardioprotection in patients having coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. (2009) 137:1436–1442.e2. doi: 10.1016/j.jtcvs.2008.04.034

52. De Hert SG, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, et al. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology*. (2004) 101:299–310. doi: 10.1097/00000542-200408000-00009

53. Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y. Immune modulation by volatile anesthetics. *Anesthesiology*. (2016) 125:399–411. doi: 10.1097/ALN.0000000000001195

54. Yuki K, Eckenhoff RG. Mechanisms of the immunological effects of volatile anesthetics: a review. *Anesth Analg*. (2016) 123:326–35. doi: 10.1213/ANE.0000000000001403

55. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, et al. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. *Anesthesiology*. (2003) 98:1315–27. doi: 10.1097/00000542-200306000-00004

56. Garcia C, Julier K, Bestmann L, Zollinger A, von Segesser LK, Pasch T, et al. Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. *Br J Anaesth*. (2005) 94:159–65. doi: 10.1093/bja/aei026

57. Uhlig C, Bluth T, Schwarz K, Deckert S, Heinrich L, De Hert S, et al. Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: a systematic review and Meta-analysis. *Anesthesiology*. (2016) 124:1230–45. doi: 10.1097/ALN.0000000000001120

58. Bonanni A, Signori A, Alicino C, Mannucci I, Grasso MA, Martinelli L, et al. Volatile anesthetics versus Propofol for cardiac surgery with cardiopulmonary bypass: Meta-analysis of randomized trials. *Anesthesiology*. (2020) 132:1429–46. doi: 10.1097/ALN.0000000000003236

59. Ștefan M, Predoi C, Goicea R, Filipescu D. Volatile Anaesthesia versus Total intravenous Anaesthesia for cardiac surgery-a narrative review. *J Clin Med*. (2022) 11:6031. doi: 10.3390/jcm11206031

60. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. (2011) 124:e652–735. doi: 10.1161/CIR.0b013e31823c074e

61. Wahba A, Milojevic M, Boer C, De Somer F, Gudbjartsson T, van den Goor J, et al. 2019 EACTS/EACTA/EBCP guidelines on cardiopulmonary bypass in adult cardiac surgery. *Eur J Cardiothorac Surg*. (2020) 57:210–51. doi: 10.1093/ejcts/ezz267

62. Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet*. (2007) 370:575–9. doi: 10.1016/S0140-6736(07)61296-3

63. Venugopal V, Hausenloy DJ, Ludman A, Di Salvo C, Kolvekar S, Yap J, et al. Remote ischaemic preconditioning reduces myocardial injury in patients undergoing

cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. *Heart*. (2009) 95:1567–71. doi: 10.1136/hrt.2008.155770

64. Thielmann M, Kottenberg E, Boengler K, Raffelsieper C, Neuhaeuser M, Peters J, et al. Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. *Basic Res Cardiol*. (2010) 105:657–64. doi: 10.1007/s00395-010-0104-5

65. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, et al. For the RenalRIPC Investigators. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery. A randomized clinical trial. *JAMA*. (2015) 313:2133–41. doi: 10.1001/jama.2015.4189

66. Zarbock A, Kellum JA, Van Aken H, Schmidt C, Küllmar M, Rosenberger P, et al. Long-term effects of remote ischemic preconditioning on kidney function in high-risk cardiac surgery patients: follow-up results from the RenalRIP trial. *Anesthesiology*. (2017) 126:787–98. doi: 10.1097/ALN.0000000000001598

67. Rahman IA, Mascaro JG, Steeds RP, Frenneaux MP, Nightingale P, Gosling P, et al. Remote ischemic preconditioning in human coronary artery bypass surgery: from promise to disappointment? *Circulation*. (2010) 122:S53–9. doi: 10.1161/CIRCULATIONAHA.109.926667

68. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, et al. For the RIPHeart study collaborators. A multicenter trial of remote ischemic preconditioning for heart surgery. *N Engl J Med*. (2015) 373:1397–407. doi: 10.1056/NEJMoa1413579

69. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, et al. For the ERICCA trial Investigators. Remote ischemic preconditioning and outcomes of cardiac surgery. *N Engl J Med*. (2015) 373:1408–17. doi: 10.1056/NEJMoa1413534

70. Hong DM, Lee EH, Kim HJ, Min JJ, Chin JH, Choi DK, et al. Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic preconditioning with Postconditioning outcome trial. *Eur Heart J*. (2014) 35:176–83. doi: 10.1093/eurheartj/eht346

71. Benstoem C, Stoppe C, Liakopoulos OJ, Ney J, Hasenclever D, Meybohm P, et al. Remote ischaemic preconditioning for coronary artery bypass grafting (with or without valve surgery). *Cochrane Database Syst Rev*. (2017) 2017:CD011719. doi: 10.1002/14651858.CD011719.pub3

72. Pierce B, Bole I, Patel V, Brown DL. Clinical outcomes of remote ischemic preconditioning prior to cardiac surgery: a Meta-analysis of randomized controlled trials. *J Am Heart Assoc*. (2017) 6:e004666. doi: 10.1161/JAHA.116.004666

73. Johnsen J, Pryds K, Salman R, Løfgren B, Kristiansen SB, Bøtker HE. The remote ischemic preconditioning algorithm: effect of number of cycles, cycle duration and effector organ mass on efficacy of protection. *Basic Res Cardiol*. (2016) 111:10. doi: 10.1007/s00395-016-0529-6

74. Meersch M, Küllmar M, Pavenstädt H, Rossaint J, Kellum JA, Martens S, et al. Effects of different doses of remote ischemic preconditioning on kidney damage among patients undergoing cardiac surgery: a single-center mechanistic randomized controlled trial. *Crit Care Med*. (2020) 48:e690–7. doi: 10.1097/CCM.0000000000004415

75. Candilio L, Malik A, Ariti C, Barnard M, Di Salvo C, Lawrence D, et al. Effect of remote ischaemic preconditioning on clinical outcomes in patients undergoing cardiac bypass surgery: a randomised controlled clinical trial. *Heart*. (2015) 101:185–92. doi: 10.1136/heartjnl-2014-306178

76. Hamarneh A, Ho AFW, Bulluck H, Sivaraman V, Ricciardi F, Nicholas J, et al. Negative interaction between nitrates and remote ischemic preconditioning in patients undergoing cardiac surgery: the ERIC-GTN and ERICCA studies. *Basic Res Cardiol*. (2022) 117:31. doi: 10.1007/s00395-022-00938-3

77. Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G, et al. Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol - a clinical trial. *Acta Anaesthesiol Scand*. (2012) 56:30–8. doi: 10.1111/j.1399-6576.2011.02585.x

78. Smul TM, Stumpner J, Blomeyer C, Lotz C, Redel A, Lange M, et al. Propofol inhibits desflurane-induced preconditioning in rabbits. *J Cardiothorac Vasc Anesth*. (2011) 25:276–81. doi: 10.1053/j.jvca.2010.07.018

79. Behmenburg F, van Caster P, Bunte S, Brandenburger T, Heinen A, Hollmann MW, et al. Impact of anesthetic regimen on remote ischemic preconditioning in the rat heart in vivo. *Anesth Analg*. (2018) 126:1377–80. doi: 10.1213/ANE.0000000000002563

80. Long YQ, Feng XM, Shan XS, Chen QC, Xia Z, Ji FH, et al. Remote ischemic preconditioning reduces acute kidney injury after cardiac surgery: a systematic review and Meta-analysis of randomized controlled trials. *Anesth Analg*. (2022) 134:592–605. doi: 10.1213/ANE.0000000000005804

81. Doenst T, Wijeysundera D, Karkouti K, Zechner C, Maganti M, Rao V, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg*. (2005) 130:1144.e1–8. doi: 10.1016/j.jtcvs.2005.05.049

82. Ouattara A, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology*. (2005) 103:687–94. doi: 10.1097/00000542-200510000-00006

83. Ascione R, Rogers CA, Rajakaruna C, Angelini GD. Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. *Circulation*. (2008) 118:113–23. doi: 10.1161/CIRCULATIONAHA.107.706416

84. Gross ER, LaDisa JF Jr, Weihrauch D, Olson LE, Kress TT, Hettrick DA, et al. Reactive oxygen species modulate coronary wall shear stress and endothelial function during hyperglycemia. *Am J Physiol Heart Circ Physiol*. (2003) 284:H1552–9. doi: 10.1152/ajpheart.01013.2002

85. Amour J, Brzezinska AK, Jager Z, Sullivan C, Weihrauch D, Du J, et al. Hyperglycemia adversely modulates endothelial nitric oxide synthase during anesthetic preconditioning through tetrahydrobiopterin- and heat shock protein 90-mediated mechanisms. *Anesthesiology*. (2010) 112:576–85. doi: 10.1097/ALN.0b013e3181cded1f

86. Mapanga RF, Essop MF. Damaging effects of hyperglycemia on cardiovascular function: spotlight on glucose metabolic pathways. *Am J Physiol Heart Circ Physiol*. (2016) 310:H153–73. doi: 10.1152/ajpheart.00206.2015

87. Kersten JR, Toller WG, Gross ER, Pagel PS, Warltier DC. Diabetes abolishes ischemic preconditioning: role of glucose, insulin, and osmolality. *Am J Physiol Heart Circ Physiol*. (2000) 278:H1218–24. doi: 10.1152/ajpheart.2000.278.4.H1218

88. Kehl F, Krolikowski JG, Mraovic B, Pagel PS, Warltier DC, Kersten JR. Hyperglycemia prevents isoflurane-induced preconditioning against myocardial infarction. *Anesthesiology*. (2002) 96:183–8. doi: 10.1097/00000542-200201000-00032

89. Huhn R, Heinen A, Weber NC, Hollmann MW, Schlack W, Preckel B. Hyperglycaemia blocks sevoflurane-induced postconditioning in the rat heart in vivo: cardioprotection can be restored by blocking the mitochondrial permeability transition pore. *Br J Anaesth*. (2008) 100:465–71. doi: 10.1093/bja/aen022

90. Canfield SG, Zaja I, Godshaw B, Twaroski D, Bai X, Bosnjak ZJ. High glucose attenuates anesthetic Cardioprotection in stem-cell-derived cardiomyocytes: the role of reactive oxygen species and mitochondrial fission. *Anesth Analg*. (2016) 122:1269–79. doi: 10.1213/ANE.0000000000001254

91. Jonassen AK, Sack MN, Mjos OD, Yellon DM. Myocardial protection by insulin at reperfusion requires early administration and is mediated via Akt and p70s6 kinase cell-survival signaling. *Circ Res*. (2001) 89:1191–8. doi: 10.1161/hh2401.101385

92. Sack MN, Yellon DM. Insulin therapy as an adjunct to reperfusion after acute coronary ischemia: a proposed direct myocardial cell survival effect independent of metabolic modulation. *J Am Coll Cardiol*. (2003) 41:1404–7. doi: 10.1016/s0735-1097(03)00164-5

93. Ng KW, Allen ML, Desai A, Macrae D, Pathan N. Cardioprotective effects of insulin: how intensive insulin therapy may benefit cardiac surgery patients. *Circulation*. (2012) 125:721–8. doi: 10.1161/CIRCULATIONAHA.111.063784

94. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. (2003) 125:1007–21. doi: 10.1067/mtc.2003.181

95. Subramaniam B, Panzica PJ, Novack V, Mahmood F, Matyal R. Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. *Anesthesiology*. (2009) 110:970–7. doi: 10.1097/ALN.0b013e3181a1005b

96. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. (2006) 105:244–52. doi: 10.1097/00000542-200608000-00006

97. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. (2001) 345:1359–67. doi: 10.1056/NEJMoa011300

98. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med*. (2007) 146:233–43. doi: 10.7326/0003-4819-146-4-200702200-00002

99. Saager L, Duncan AE, Yared JP, Hesler BD, You J, Deogaonkar A, et al. Intraoperative tight glucose control using hyperinsulinemic normoglycemia increases delirium after cardiac surgery. *Anesthesiology*. (2015) 122:1214–23. doi: 10.1097/ALN.0000000000000669

100. Duncan AE, Abd-Elsayed A, Maheshwari A, Xu M, Soltesz E, Koch CG. Role of intraoperative and postoperative blood glucose concentrations in predicting outcomes after cardiac surgery. *Anesthesiology*. (2010) 112:860–71. doi: 10.1097/ALN.0b013e3181d3d4b4

101. Duncan AE, Sessler DI, Sato H, Sato T, Nakazawa K, Carvalho G, et al. Hyperinsulinemic normoglycemia during cardiac surgery reduces a composite of 30-day mortality and serious in-hospital complications: a randomized clinical trial. *Anesthesiology*. (2018) 128:1125–39. doi: 10.1097/ALN.0000000000002156

102. Lazar HL, McDonnell M, Chipkin SR, Furnary AP, Engelman RM, Sadhu AR, et al. Society of Thoracic Surgeons blood glucose guideline task force. The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. *Ann Thorac Surg*. (2009) 87:663–9. doi: 10.1016/j.athoracsur.2008.11.011

103. Sebranek JJ, Lugli AK, Coursin DB. Glycaemic control in the perioperative period. *Br J Anaesth*. (2013) 111:i18–34. doi: 10.1093/bja/aet381

104. Reddy P, Duggar B, Butterworth J. Blood glucose management in the patient undergoing cardiac surgery: a review. *World J Cardiol*. (2014) 6:1209–17. doi: 10.4330/wjc.v6.i11.1209

105. Duggan EW, Carlson K, Umpierrez GE. Perioperative hyperglycemia management: an update. *Anesthesiology*. (2017) 126:547–60. doi: 10.1097/ALN.0000000000001515

106. Galindo RJ, Fayfman M, Umpierrez GE. Perioperative Management of Hyperglycemia and Diabetes in cardiac surgery patients. *Endocrinol Metab Clin N Am*. (2018) 47:203–22. doi: 10.1016/j.ecl.2017.10.005

107. Zweier JL, Talukder MA. The role of oxidants and free radicals in reperfusion injury. *Cardiovasc Res*. (2006) 70:181–90. doi: 10.1016/j.cardiores.2006.02.025

108. Peng YW, Mohammed A, Deatrick KB, Major T, Cheng D, Charpie I, et al. Differential effects of normoxic and Hyperoxic reperfusion on global myocardial ischemia-reperfusion injury. *Semin Thorac Cardiovasc Surg*. (2019) 31:188–98. doi: 10.1053/j.semtcvs.2018.09.018

109. Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. *J Am Coll Cardiol*. (2010) 56:1013–6. doi: 10.1016/j.jacc.2010.04.052

110. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J*. (2009) 158:371–7. doi: 10.1016/j.ahj.2009.05.037

111. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N. Et al; DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. *N Engl J Med*. (2017) 377:1240–9. doi: 10.1056/NEJMoa1706222

112. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation*. (2015) 131:2143–50. doi: 10.1161/CIRCULATIONAHA.114.014494

113. Sepehrvand N, James SK, Stub D, Khoshnood A, Ezekowitz JA, Hofmann R. Effects of supplemental oxygen therapy in patients with suspected acute myocardial infarction: a meta-analysis of randomised clinical trials. *Heart*. (2018) 104:1691–8. doi: 10.1136/heartjnl-2018-313089

114. Ferrando C, Soro M, Belda FJ. Protection strategies during cardiopulmonary bypass: ventilation, anesthetics and oxygen. *Curr Opin Anaesthesiol*. (2015) 28:73–80. doi: 10.1097/ACO.0000000000000143

115. Heinrichs J, Grocott HP. Pro: Hyperoxia should be used during cardiac surgery. *J Cardiothorac Vasc Anesth*. (2019) 33:2070–4. doi: 10.1053/j.jvca.2018.02.015

116. Roberts SM, Cios TJ. Con: Hyperoxia should not be used routinely in the Management of Cardiopulmonary Bypass. *J Cardiothorac Vasc Anesth*. (2019) 33:2075–8. doi: 10.1053/j.jvca.2019.02.027

117. Caputo M, Mokhtari A, Miceli A, Ghorbel MT, Angelini GD, Parry AJ, et al. Controlled reoxygenation during cardiopulmonary bypass decreases markers of organ damage, inflammation, and oxidative stress in single-ventricle patients undergoing pediatric heart surgery. *J Thorac Cardiovasc Surg*. (2014) 148:792–801.e8. doi: 10.1016/j.jtcvs.2014.06.001

118. Ihnken K, Winkler A, Schlensak C, Sarai K, Neidhart G, Unkelbach U, et al. Normoxic cardiopulmonary bypass reduces oxidative myocardial damage and nitric oxide during cardiac operations in the adult. *J Thorac Cardiovasc Surg*. (1998) 116:327–34. doi: 10.1016/s0022-5223(98)70134-5

119. Inoue T, Ku K, Kaneda T, Zang Z, Otaki M, Oku H. Cardioprotective effects of lowering oxygen tension after aortic unclamping on cardiopulmonary bypass during coronary artery bypass grafting. *Circ J*. (2002) 66:718–22. doi: 10.1253/circj.66.718

120. McGuinness SP, Parke RL, Drummond K, Willcox T, Bailey M, Kruger C, et al. SO-COOL investigators. A multicenter, randomized, controlled phase IIb trial of avoidance of Hyperoxemia during cardiopulmonary bypass. *Anesthesiology*. (2016) 125:465–73. doi: 10.1097/ALN.0000000000001226

121. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB, Shotwell MS, et al. Intraoperative oxidative damage and delirium after cardiac surgery. *Anesthesiology*. (2020) 132:551–61. doi: 10.1097/ALN.0000000000003016

122. Cobbe SM, Poole-Wilson PA. The time of onset and severity of acidosis in myocardial ischaemia. *J Mol Cell Cardiol*. (1980) 12:745–60. doi: 10.1016/0022-2828(80)90077-2

123. Currin RT, Gores GJ, Thurman RG, Lemasters JJ. Protection by acidotic pH against anoxic cell killing in perfused rat liver: evidence for a pH paradox. *FASEB J*. (1991) 5:207–10. doi: 10.1096/fasebj.5.2.2004664

124. Bond JM, Harper IS, Chacon E, Reece JM, Herman B, Lemasters JJ. The pH paradox in the pathophysiology of reperfusion injury to rat neonatal cardiac myocytes. *Ann N Y Acad Sci*. (1994) 723:25–37. doi: 10.1111/j.1749-6632.1994.tb36714.x

125. Kitakaze M, Takashima S, Funaya H, Minamino T, Node K, Shinozaki Y, et al. Temporary acidosis during reperfusion limits myocardial infarct size in dogs. *Am J Phys*. (1997) 272:H2071–8. doi: 10.1152/ajpheart.1997.272.5.H2071

126. Kim JS, Jin Y, Lemasters JJ. Reactive oxygen species, but not Ca2+ overloading, trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemia-reperfusion. *Am J Physiol Heart Circ Physiol*. (2006) 290:H2024–34. doi: 10.1152/ajpheart.00683.2005

127. Kaplan SH, Yang H, Gilliam DE, Shen J, Lemasters JJ, Cascio WE. Hypercapnic acidosis and dimethyl amiloride reduce reperfusion induced cell death in ischaemic ventricular myocardium. *Cardiovasc Res*. (1995) 29:231–8. doi: 10.1016/S0008-6363(96)88575-0

128. Ohashi T, Yamamoto F, Yamamoto H, Ichikawa H, Shibata T, Kawashima Y. Transient reperfusion with acidic solution affects postischemic functional recovery: studies in the isolated working rat heart. *J Thorac Cardiovasc Surg*. (1996) 111:613–20. doi: 10.1016/s0022-5223(96)70313-6

129. Inserte J, Barba I, Hernando V, Abellán A, Ruiz-Meana M, Rodríguez-Sinovas A, et al. Effect of acidic reperfusion on prolongation of intracellular acidosis and myocardial salvage. *Cardiovasc Res*. (2008) 77:782–90. doi: 10.1093/cvr/cvm082

130. Fujita M, Asanuma H, Hirata A, Wakeno M, Takahama H, Sasaki H, et al. Prolonged transient acidosis during early reperfusion contributes to the cardioprotective effects of postconditioning. *Am J Physiol Heart Circ Physiol*. (2007) 292:H2004–8. doi: 10.1152/ajpheart.01051.2006

131. Cohen MV, Yang XM, Downey JM. The pH hypothesis of postconditioning: staccato reperfusion reintroduces oxygen and perpetuates myocardial acidosis. *Circulation*. (2007) 115:1895–903. doi: 10.1161/CIRCULATIONAHA.106.675710

132. Inserte J, Barba I, Hernando V, Garcia-Dorado D. Delayed recovery of intracellular acidosis during reperfusion prevents calpain activation and determines protection in postconditioned myocardium. *Cardiovasc Res*. (2009) 81:116–22. doi: 10.1093/cvr/cvn260

133. Inserte J, Ruiz-Meana M, Rodríguez-Sinovas A, Barba I, Garcia-Dorado D. Contribution of delayed intracellular pH recovery to ischemic postconditioning protection. *Antioxid Redox Signal*. (2011) 14:923–39. doi: 10.1089/ars.2010.3312

134. Hartmann M, Decking UK. Blocking Na(+)-H+ exchange by cariporide reduces Na(+)-overload in ischemia and is cardioprotective. *J Mol Cell Cardiol*. (1999) 31:1985–95. doi: 10.1006/jmcc.1999.1029

135. Avkiran M, Marber MS. Na(+)/H(+) exchange inhibitors for cardioprotective therapy: progress, problems and prospects. *J Am Coll Cardiol*. (2002) 39:747–53. doi: 10.1016/s0735-1097(02)01693-5

136. Strömer H, de Groot MC, Horn M, Faul C, Leupold A, Morgan JP, et al. Na(+)/H(+) exchange inhibition with HOE642 improves postischemic recovery due to attenuation of ca(2+) overload and prolonged acidosis on reperfusion. *Circulation*. (2000) 101:2749–55. doi: 10.1161/01.cir.101.23.2749

137. Mentzer RM Jr, Bartels C, Bolli R, Boyce S, Buckberg GD, Chaitman B, et al. EXPEDITION study Investigators. Sodium-hydrogen exchange inhibition by cariporide to reduce the risk of ischemic cardiac events in patients undergoing coronary artery bypass grafting: results of the EXPEDITION study. *Ann Thorac Surg*. (2008) 85:1261–70. doi: 10.1016/j.athoracsur.2007.10.054

138. Okamoto F, Allen BS, Buckberg GD, Bugyi H, Leaf J. Reperfusion conditions: importance of ensuring gentle versus sudden reperfusion during relief of coronary occlusion. *J Thorac Cardiovasc Surg*. (1986) 92:613–20. doi: 10.1016/S0022-5223(19)36512-2

139. Hori M, Kitakaze M, Sato H, Takashima S, Iwakura K, Inoue M, et al. Staged reperfusion attenuates myocardial stunning in dogs. Role of transient acidosis during early reperfusion. *Circulation*. (1991) 84:2135–45. doi: 10.1161/01.cir.84.5.2135

140. Peng CF, Murphy ML, Colwell K, Straub KD. Controlled versus hyperemic flow during reperfusion of jeopardized ischemic myocardium. *Am Heart J*. (1989) 117:515–22. doi: 10.1016/0002-8703(89)90723-0

141. Bopassa JC, Michel P, Gateau-Roesch O, Ovize M, Ferrera R. Low-pressure reperfusion alters mitochondrial permeability transition. *Am J Physiol Heart Circ Physiol*. (2005) 288:H2750–5. doi: 10.1152/ajpheart.01081.2004

142. Bopassa JC, Ferrera R, Gateau-Roesch O, Couture-Lepetit E, Ovize M. PI 3-kinase regulates the mitochondrial transition pore in controlled reperfusion and postconditioning. *Cardiovasc Res*. (2006) 69:178–85. doi: 10.1016/j.cardiores.2005.07.014

143. Lindal S, Gunnes S, Lund I, Straume BK, Jørgensen L, Sørlie D. Myocardial and microvascular injury following coronary surgery and its attenuation by mode of reperfusion. *Eur J Cardiothorac Surg*. (1995) 9:83–9. doi: 10.1016/s1010-7940(05)80024-7

144. Beyersdorf F. The use of controlled reperfusion strategies in cardiac surgery to minimize ischaemia/reperfusion damage. *Cardiovasc Res*. (2009) 83:262–8. doi: 10.1093/cvr/cvp110

145. Williams JB, Hernandez AF, Li S, Dokholyan RS, O'Brien SM, Smith PK, et al. Postoperative inotrope and vasopressor use following CABG: outcome data from the CAPS-care study. *J Card Surg*. (2011) 26:572–8. doi: 10.1111/j.1540-8191.2011.01301.x

146. Belletti A, Castro ML, Silvetti S, Greco T, Biondi-Zoccai G, Pasin L, et al. The effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. *Br J Anaesth*. (2015) 115:656–75. doi: 10.1093/bja/aev284

147. Fellahi JL, Fischer MO, Daccache G, Gerard JL, Hanouz JL. Positive inotropic agents in myocardial ischemia-reperfusion injury: a benefit/risk analysis. *Anesthesiology*. (2013) 118:1460–5. doi: 10.1097/ALN.0b013e31828f4fc3

148. Fellahi JL, Parienti JJ, Hanouz JL, Plaud B, Riou B, Ouattara A. Perioperative use of dobutamine in cardiac surgery and adverse cardiac outcome: propensity-adjusted analyses. *Anesthesiology*. (2008) 108:979–87. doi: 10.1097/ALN.0b013e318173026f

149. Nielsen DV, Hansen MK, Johnsen SP, Hansen M, Hindsholm K, Jakobsen CJ. Health outcomes with and without use of inotropic therapy in cardiac surgery: results of a propensity score-matched analysis. *Anesthesiology*. (2014) 120:1098–108. doi: 10.1097/ALN.0000000000000224

150. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol*. (2005) 46:1425–33. doi: 10.1016/j.jacc.2005.05.086

151. Ouattara A, Benhaoua H, Le Manach Y, Mabrouk-Zerguini N, Itani O, Osman A, et al. Perioperative statin therapy is associated with a significant and dose-dependent reduction of adverse cardiovascular outcomes after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth*. (2009) 23:633–8. doi: 10.1053/j.jvca.2009.02.008

152. Ludman AJ, Hausenloy DJ, Babu G, Hasleton J, Venugopal V, Boston-Griffiths E, et al. Failure to recapture cardioprotection with high-dose atorvastatin in coronary artery bypass surgery: a randomised controlled trial. *Basic Res Cardiol*. (2011) 106:1387–95. doi: 10.1007/s00395-011-0209-5

153. Allah EA, Kamel EZ, Osman HM, Abd-Elshafy SK, Nabil F, Elmelegy TTH, et al. Could short-term perioperative high-dose atorvastatin offer antiarrhythmic and cardioprotective effects in rheumatic valve replacement surgery? *J Cardiothorac Vasc Anesth*. (2019) 33:3340–7. doi: 10.1053/j.jvca.2019.05.013

154. Liakopoulos OJ, Kuhn EW, Hellmich M, Schlömicher M, Strauch J, Reents W, et al. StaRT-CABG Investigators. Statin loading before coronary artery bypass grafting: a randomized trial. *Eur Heart J*. (2023) 44:2322–31. doi: 10.1093/eurheartj/ehad238

155. Le Manach Y, Godet G, Coriat P, Martinon C, Bertrand M, Fléron MH, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg*. (2007) 104:1326–33. doi: 10.1213/01.ane.0000263029.72643.10

156. Le Manach Y, Coriat P, Collard CD, Riedel B. Statin therapy within the perioperative period. *Anesthesiology*. (2008) 108:1141–6. doi: 10.1097/ALN.0b013e318173ef8e

157. Boengler K, Schulz R, Heusch G. Loss of cardioprotection with ageing. *Cardiovasc Res*. (2009) 83:247–61. doi: 10.1093/cvr/cvp033

158. Lesnefsky EJ, Moghaddas S, Tandler B, Kerner J, Hoppel CL. Mitochondrial dysfunction in cardiac disease: ischemia--reperfusion, aging, and heart failure. *J Mol Cell Cardiol*. (2001) 33:1065–89. doi: 10.1006/jmcc.2001.1378

159. Taylor RP, Starnes JW. Age, cell signalling and cardioprotection. *Acta Physiol Scand*. (2003) 178:107–16. doi: 10.1046/j.1365-201X.2003.01132.x

160. Schulman D, Latchman DS, Yellon DM. Effect of aging on the ability of preconditioning to protect rat hearts from ischemia-reperfusion injury. *Am J Physiol Heart Circ Physiol*. (2001) 281:H1630–6. doi: 10.1152/ajpheart.2001.281.4.H1630

161. Sniecinski R, Liu H. Reduced efficacy of volatile anesthetic preconditioning with advanced age in isolated rat myocardium. *Anesthesiology*. (2004) 100:589–97. doi: 10.1097/00000542-200403000-00019

162. Lee TM, Su SF, Tsai CC, Lee YT, Tsai CH. Cardioprotective effects of 17 beta-estradiol produced by activation of mitochondrial ATP-sensitive K(+)channels in canine hearts. *J Mol Cell Cardiol*. (2000) 32:1147–58. doi: 10.1006/jmcc.2000.1167

163. Kim YD, Chen B, Beauregard J, Kouretas P, Thomas G, Farhat MY, et al. 17 beta-estradiol prevents dysfunction of canine coronary endothelium and myocardium and reperfusion arrhythmias after brief ischemia/reperfusion. *Circulation*. (1996) 94:2901–8. doi: 10.1161/01.cir.94.11.2901

164. Miyawaki H, Wang Y, Ashraf M. Oxidant stress with hydrogen peroxide attenuates calcium paradox injury: role of protein kinase C and ATP-sensitive potassium channel. *Cardiovasc Res*. (1998) 37:691–9. doi: 10.1016/s0008-6363(97)00249-6

165. Node K, Kitakaze M, Kosaka H, Minamino T, Funaya H, Hori M. Amelioration of ischemia- and reperfusion-induced myocardial injury by 17beta-estradiol: role of nitric oxide and calcium-activated potassium channels. *Circulation*. (1997) 96:1953–63. doi: 10.1161/01.cir.96.6.1953

166. Wang C, Chiari PC, Weihrauch D, Krolikowski JG, Warltier DC, Kersten JR, et al. Gender-specificity of delayed preconditioning by isoflurane in rabbits: potential role of endothelial nitric oxide synthase. *Anesth Analg*. (2006) 103:274–80. doi: 10.1213/01.ANE.0000230389.76351.0C

167. Song X, Li G, Vaage J, Valen G. Effects of sex, gonadectomy, and oestrogen substitution on ischaemic preconditioning and ischaemia-reperfusion injury in mice. *Acta Physiol Scand*. (2003) 177:459–66. doi: 10.1046/j.1365-201X.2003.01068.x

168. Tanaka K, Kersten JR, Riess ML. Opioid-induced cardioprotection. *Curr Pharm Des*. (2014) 20:5696–705. doi: 10.2174/1381612820666140204120311

169. Headrick JP, See Hoe LE, Du Toit EF, Peart JN. Opioid receptors and cardioprotection - 'opioidergic conditioning' of the heart. *Br J Pharmacol*. (2015) 172:2026–50. doi: 10.1111/bph.13042

170. Irwin MG, Wong GT. Remifentanil and opioid-induced cardioprotection. *J Cardiothorac Vasc Anesth*. (2015) 29:S23–6. doi: 10.1053/j.jvca.2015.01.021

171. Patel HH, Ludwig LM, Fryer RM, Hsu AK, Warltier DC, Gross GJ. Delta opioid agonists and volatile anesthetics facilitate cardioprotection via potentiation of K(ATP) channel opening. *FASEB J*. (2002) 16:1468–70. doi: 10.1096/fj.02-0170fje

172. Ludwig LM, Patel HH, Gross GJ, Kersten JR, Pagel PS, Warltier DC. Morphine enhances pharmacological preconditioning by isoflurane: role of mitochondrial K(ATP) channels and opioid receptors. *Anesthesiology*. (2003) 98:705–11. doi: 10.1097/00000542-200303000-00019

173. Lucchinetti E, Lou PH, Gandhi M, Clanachan AS, Zaugg M. Differential effects of anesthetics and opioid receptor activation on Cardioprotection elicited by reactive oxygen species-mediated Postconditioning in Sprague-Dawley rat hearts. *Anesth Analg*. (2018) 126:1739–46. doi: 10.1213/ANE.0000000000002676

174. Han J, Kim N, Joo H, Kim E. Ketamine abolishes ischemic preconditioning through inhibition of K(ATP) channels in rabbit hearts. *Am J Physiol Heart Circ Physiol*. (2002) 283:H13–21. doi: 10.1152/ajpheart.01064.2001

175. Müllenheim J, Frässdorf J, Preckel B, Thämer V, Schlack W. Ketamine, but not S(+)-ketamine, blocks ischemic preconditioning in rabbit hearts in vivo. *Anesthesiology*. (2001) 94:630–6. doi: 10.1097/00000542-200104000-00017

176. Müllenheim J, Rulands R, Wietschorke T, Frässdorf J, Preckel B, Schlack W. Late preconditioning is blocked by racemic ketamine, but not by S(+)-ketamine. *Anesth Analg*. (2001) 93:265–70. doi: 10.1097/00000539-200108000-00005

177. Barthel H, Ebel D, Müllenheim J, Obal D, Preckel B, Schlack W. Effect of lidocaine on ischaemic preconditioning in isolated rat heart. *Br J Anaesth*. (2004) 93:698–704. doi: 10.1093/bja/aeh262

178. Kaczmarek DJ, Herzog C, Larmann J, Gillmann HJ, Hildebrand R, Schmitz M, et al. Lidocaine protects from myocardial damage due to ischemia and reperfusion in mice by its antiapoptotic effects. *Anesthesiology*. (2009) 110:1041–9. doi: 10.1097/ALN.0b013e31819dabda

179. Lee EH, Lee HM, Chung CH, Chin JH, Choi DK, Chung HJ, et al. Impact of intravenous lidocaine on myocardial injury after off-pump coronary artery surgery. *Br J Anaesth*. (2011) 106:487–93. doi: 10.1093/bja/aeq416

180. Roehl AB, Funcke S, Becker MM, Goetzenich A, Bleilevens C, Rossaint R, et al. Xenon and isoflurane reduce left ventricular remodeling after myocardial infarction in the rat. *Anesthesiology*. (2013) 118:1385–94. doi: 10.1097/ALN.0b013e31828744c0

181. Schwiebert C, Huhn R, Heinen A, Weber NC, Hollmann MW, Schlack W, et al. Postconditioning by xenon and hypothermia in the rat heart in vivo. *Eur J Anaesthesiol*. (2010) 27:734–9. doi: 10.1097/EJA.0b013e328335fc4c

182. Hofland J, Ouattara A, Fellahi JL, Gruenewald M, Hazebroucq J, Ecoffey C, et al. Effect of xenon anesthesia compared to sevoflurane and Total intravenous anesthesia for coronary artery bypass graft surgery on postoperative cardiac troponin release: an international, multicenter, phase 3, single-blinded, randomized noninferiority trial. *Anesthesiology*. (2017) 127:918–33. doi: 10.1097/ALN.0000000000001873

183. Javadov S, Karmazyn M. Mitochondrial permeability transition pore opening as an endpoint to initiate cell death and as a putative target for cardioprotection. *Cell Physiol Biochem*. (2007) 20:1–22. doi: 10.1159/000103747

184. Dj H, Kunst G, Boston-Griffiths E, Kolvekar S, Chaubey S, John L, et al. The effect of cyclosporin-a on peri-operative myocardial injury in adult patients undergoing coronary artery bypass graft surgery: a randomised controlled clinical trial. *Heart*. (2014) 100:544–9. doi: 10.1136/heartjnl-2013-304845

185. Chiari P, Angoulvant D, Mewton N, Desebbe O, Obadia JF, Robin J, et al. Cyclosporine protects the heart during aortic valve surgery. *Anesthesiology*. (2014) 121:232–8. doi: 10.1097/ALN.0000000000000331

186. Cung TT, Morel O, Cayla G, Rioufol G, Garcia-Dorado D, Angoulvant D, et al. Cyclosporine before PCI in patients with acute myocardial infarction. *N Engl J Med*. (2015) 373:1021–31. doi: 10.1056/NEJMoa1505489

187. Fan Y, Yang S, Zhang X, Cao Y, Huang Y. Comparison of cardioprotective efficacy resulting from a combination of atorvastatin and ischaemic post-conditioning in diabetic and non-diabetic rats. *Clin Exp Pharmacol Physiol*. (2012) 39:938–43. doi: 10.1111/1440-1681.12014

188. Yang XM, Cui L, Alhammouri A, Downey JM, Cohen MV. Triple therapy greatly increases myocardial salvage during ischemia/reperfusion in the in situ rat heart. *Cardiovasc Drugs Ther*. (2013) 27:403–12. doi: 10.1007/s10557-013-6474-9

189. Prunier F, Angoulvant D, Saint Etienne C, Vermes E, Gilard M, Piot C, et al. The RIPOST-MI study, assessing remote ischemic perconditioning alone or in combination with local ischemic postconditioning in ST-segment elevation myocardial infarction. *Basic Res Cardiol*. (2014) 109:400. doi: 10.1007/s00395-013-0400-y

190. Eitel I, Stiermaier T, Rommel KP, Fuernau G, Sandri M, Mangner N, et al. Cardioprotection by combined intrahospital remote ischaemic perconditioning and postconditioning in ST-elevation myocardial infarction: the randomized LIPSIA CONDITIONING trial. *Eur Heart J*. (2015) 36:3049–57. doi: 10.1093/eurheartj/ehv463

191. Chiari P, Mewton N, Maucort-Boulch D, Desebbe O, Durand M, Fischer MO, et al. Multimodal strategy for myocardial protection during cardiac surgery: the ProCCard study. *J Am Coll Cardiol*. (2021) 77:827–9. doi: 10.1016/j.jacc.2020.12.020

192. Chiari P, Desebbe O, Durand M, Fischer MO, Lena-Quintard D, Palao JC, et al. A multimodal cardioprotection strategy during cardiac surgery: the ProCCard study. *J Cardiothorac Vasc Anesth*. (2023) 37:1368–76. doi: 10.1053/j.jvca.2023.04.011