Review

Preconditioning, postconditioning and their application to clinical cardiology

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Abstract

Ischemic preconditioning is a well-established phenomenon first described in experimental preparations in which brief episodes of ischemia/reperfusion applied prior to a longer coronary artery occlusion reduce myocardial infarct size. There are ample correlates of ischemic preconditioning in the clinical realm. Preconditioning mimetic agents that stimulate the biochemical pathways of ischemic preconditioning and protect the heart without inducing ischemia have been examined in numerous experimental studies. However, despite the effectiveness of ischemic preconditioning and preconditioning mimetics for protecting ischemic myocardium, there are no preconditioning-based therapies that are routinely used in clinical medicine at the current time. Part of the problem is the need to administer therapy prior to the known ischemic event. Other issues are that percutaneous coronary intervention technology has advanced so far (with the development of stents and drug-eluting stents) that ischemic preconditioning or preconditioning mimetics have not been needed in most interventional cases. Recent clinical trials such as AMISTAD I and II (Acute Myocardial Infarction STudy of ADenosine) suggest that some preconditioning mimetics may reduce myocardial infarct size when given along with reperfusion or, as in the IONA trial, have benefit on clinical events when administered chronically in patients with known coronary artery disease. It is possible that some of the benefit described for adenosine in the AMISTAD 1 and 2 trials represents a manifestation of the recently described postconditioning phenomenon. It is probable that postconditioning – in which reperfusion is interrupted with brief coronary occlusions and reperfusion sequences – is more likely than preconditioning to be feasible as a clinical application to patients undergoing percutaneous coronary intervention for acute myocardial infarction.

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1. Ischemic preconditioning

Ischemic preconditioning is clearly one of the most reproducible and powerful cardioprotective maneuvers for reducing experimental myocardial infarct size [1–4]. There is strong evidence that this phenomenon occurs in the human heart as recently reviewed [3,4]. Manifestations of preconditioning in the human heart include the observations that isolated human cells and isolated human trabeculae recapitulate preconditioning behaviors in experimental in vitro preparations; that repeat angioplasty balloon inflations result in less chest pain, ST segment elevation, and lactate production than upon an initial inflation; that a second episode of ischemia induced by exercise or pacing is associated with less chest pain, ST segment change, and lactate production than a first episode; that preinfarct angina reduces infarct size and is associated with better clinical outcome; that intermittent aortic cross clamping preserves myocardial ATP during coronary artery bypass surgery; and

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that certain preconditioning mimetic agents can reduce ischemia during balloon inflation or exercise testing in both an early preconditioning and delayed fashion [3–5]. Despite evidence that preconditioning works in both animal models and humans, the concept simply has not been applied to routine therapy in clinical medicine. The following review will focus on potential clinical applications of preconditioning as they relate to recent clinical trials and then discuss the potential of postconditioning for clinical therapy.

2. Clinical application of ischemic preconditioning

2.1. Cardiac surgery

For true ischemic preconditioning to be applied clinically the therapy must be applied prior to the prolonged episode of ischemia. Application of brief episodes of ischemia to the heart prior to cardiopulmonary bypass affords an opportune application of ischemic preconditioning since the exact moment that the heart is placed on bypass is known. Yellon et al. [6] showed that brief intermittent aortic cross-clamping prior to coronary artery bypass surgery preserved adenosine triphosphate levels of myocardial biopsy specimens.

Since Yellon’s original observation, several other groups have verified the finding that the human heart undergoing cardiac surgery can be preconditioned. The findings are not unique to coronary artery bypass grafting surgery. Lu et al. [7] studied 30 patients who were undergoing aortic and mitral valve replacement for rheumatic valve disease. Ischemic preconditioning was induced with two episodes of 2-min occlusions of the vena cava and aorta with 3 min of reperfusion. Hearts were arrested at 4 °C and cold crystalloid cardioplegia was administered. At 90 min of cardiac arrest the adenosine triphosphate level of the heart was higher in the preconditioned group than controls and there was less release of creatine kinase from the preconditioned hearts. In addition at 30 min after reperfusion following cardiopulmonary bypass the left ventricular contractility was greater in preconditioned hearts (dP/dt=1490 mmHg/s) versus control hearts (dP/dt=1250 mmHg/s, P<0.05). These results extended the work of Yellon by verifying that preconditioning protected hearts undergoing valvular surgery and improved post-bypass functional recovery. On the other hand, in a preclinical study comparing ischemic preconditioning to cardioplegia, Kolocassides et al. [7a] observed that preconditioning protected post-ischemic contractile function and reduced cellular acidosis but actually accelerated ischemic contracture and depletion of ATP. Cardioplegia slowed depletion of ATP, contracture and delayed onset of acidosis and improved postischemic force. Hence there remains some controversy regarding the benefits of preconditioning versus cardioplegia.

Teoh et al. [8] from Yellon’s group again showed that two 3-min periods of ischemia followed by 2 min of reperfusion decreased troponin T release following ~90 min of cardiopulmonary bypass in patients undergoing coronary artery bypass surgery. An adenosine A1 receptor agonist (GR79236X) failed to protect the myocardium in this study, suggesting that in the setting of coronary artery bypass surgery preconditioning may rely upon other pathways.

Wu et al. [9] studied a potential mechanism of ischemic preconditioning in patients undergoing coronary artery bypass surgery. They studied 40 patients undergoing coronary artery bypass grafting who were randomized to ischemic preconditioning consisting of two cycles of 2 min of ischemia followed by 3 min of reperfusion prior to cross clamping or control. Free radicals were measured in coronary sinus blood using spin-trap spectroscopy. The ischemic preconditioning protocol itself resulted in a 5.6% increase in free radical content. At 10 min following declamping the aorta, there were increases in free radicals in the coronary sinus of both groups (~8%). At 1 and 6 h following aortic declamping left ventricular function was improved in the ischemic preconditioning group versus controls. Left ventricular stroke work index at 1 and 6 h after declamping correlated with free radical generation after the ischemic preconditioning protocol in the preconditioning group. The authors concluded that free radical generation during the ischemic preconditioning phase serves as a trigger for ischemic preconditioning.

As mentioned above, there are many studies that suggest that preinfarct angina may function as an ischemic preconditioning stimulus [2–5,10–14]. Can patients undergoing coronary artery bypass grafting be conditioned with ischemia/reperfusion cycles prior to cross-clamping if they have experienced recent angina (and therefore may already be preconditioned)? Wu and coworkers [15] studied 40 patients undergoing coronary artery bypass surgery who were randomized to control (n=20) or ischemic preconditioning (n=20). Those patients who had angina within 48 h prior to surgery had no improvement of cardiac index or right ventricular ejection fraction with the preclamping ischemic preconditioning protocol. In contrast, those patients who had angina at 48–72 h prior to surgery did demonstrate improved cardiac index and right ventricular ejection fraction with the preconditioning protocol versus controls. These data suggest that a pre-surgical preconditioning protocol could improve cardiac function following cardiopulmonary bypass if angina had occurred 48–72 h prior to surgery but not if angina had occurred within 48 h of surgery. Thus, it is possible that patients with recent angina may already have been preconditioned to some extent.

A recent study [16] also suggested that ischemic preconditioning could benefit patients undergoing minimally invasive coronary artery bypass surgery without cardiopulmonary bypass or cardioplegia. Ischemic preconditioning was induced with a brief coronary artery occlusion/reperfusion. Ischemic preconditioning minimized anisotropy and QT and JT dispersions suggesting that ischemic preconditioning provided antiarrhythmic properties in the setting of minimally invasive coronary artery bypass surgery.
Several studies show that human myocardium can be preconditioned [17–20]. However, one study [21] suggested that pathologic human myocardium – diabetic or failing human right atrial appendage – did not benefit from simulated in vitro ischemic preconditioning protocols.

While ischemic preconditioning protocols were shown to be effective by a number of groups for preserving myocardial ATP, enzymes, and improving function, the concept has not translated to routine clinical practice for most surgical groups. Why is this, given the relative ease of treatment? In discussing this with cardiac surgeons we heard several opinions. One was concern about intermittent clamping and unclamping of the aorta-inducing distal embolization of atherosclerotic plaque debris. The same concern can be raised for brief coronary artery occlusion/reperfusion sequences in minimally invasive coronary artery bypass surgery. Another concern was the concept that current cardioplegic techniques were adequate enough to protect the myocardium during the surgical procedure. Monitoring the status of the myocardium with PH probes and temperature probes may allow better protection of this tissue during cardiopulmonary bypass. Targeting the molecular mechanisms of ischemic preconditioning without actually inducing ischemia is perhaps a safer technique and will be discussed below.

2.2. Myocardial infarction

Numerous studies have shown that preinfarct angina confers protection in patients who develop acute myocardial infarction [2–5,10–14], and at least some of this benefit may be a preconditioning phenomenon rather than simply recruiting collateral blood flow. Preinfarct angina has been associated with smaller myocardial infarct size, less congestive heart failure, less cardiac death, fewer arrhythmias, and improved cardiac function as recently reviewed [3]. While some investigations suggested that the benefit was lost in elderly patients [22], other studies showed a benefit of preinfarct angina even in older patients [23]. It has also been suggested that an exercise protocol may re-establish the benefits of ischemic preconditioning in the elderly [24,25]. The concept of trying to treat acute myocardial infarction with ischemia prior to the infarct is a nearly impossible approach, since predicting when an acute myocardial infarction will occur is not possible. However, it might be possible to treat high-risk patients or patients with unstable angina with preconditioning mimetic agents, agents that simulate the biochemistry of preconditioning without actually causing ischemia.

2.3. Percutaneous coronary intervention

As previously reviewed, repetitive brief angioplasty balloon inflations and deflations in a coronary artery will precondition the myocardium [5]. Several angioplasty studies demonstrated that this approach reduced chest pain, ST segment elevation, CK release, and lactate levels [26–29]. As described below, preconditioning mimetic agents also can impart these benefits. However, is this approach part of the standard of care among interventional cardiologists? In general, no. The technology of percutaneous coronary intervention has advanced to the point where balloon angioplasty now coupled with stenting requires arterial occlusion for about 20–30 s, hardly producing significant ischemia. Stents have made a big difference in this regard, so rarely will protection of the distal myocardium during a procedure be needed. In addition, distal perfusion catheters were developed that allowed flow of blood to distal myocardium through the catheter, even when the balloon is inflated. Thus, at the present time, although ischemic preconditioning could be useful to high-risk percutaneous coronary intervention, it is rarely needed or used. Nevertheless, balloon angioplasty may serve as a useful model to test various preconditioning mimetic agents.

2.4. Transplantation

Ischemic preconditioning could be used to protect the ischemic heart following removal for transplantation [30,31]. However, again it is rarely used. Current cooling techniques and preserving fluids are thought by most to be adequate.

2.5. Warm-up

The warm-up phenomenon has been described to be a manifestation of ischemic preconditioning. Studies showed that exercise tolerance for ischemia was improved on a second exercise test compared to a first one (where the tests were separated by a 10–15 min period of rest) [32–36]. A practical and easily applied lesson from this observation is that patients with known coronary artery disease should warm-up prior to exercise. Preconditioning mimetic agents also might be considered in this context. We liberally administer short acting nitroglycerin in a prophylactic manner to patients with exercise-induced angina. Taking a sublingual nitroglycerin 5–10 min prior to planned exertion may blunt or totally prevent angina associated with this activity. This observation may be unrelated to preconditioning and may simply be due to the fact that acute nitroglycerin acts as a preload and afterload reducer and in addition dilates the coronary arteries, thus reducing oxygen demand at the same time it improves oxygen supply. Since NO has now been implicated in triggering classical or early phase preconditioning [37,38], nitroglycerin – an NO donor – may act to reduce additional ischemic episodes acutely via a preconditioning mechanism. In addition, recent studies suggest that nitroglycerin may have an added benefit, that of a delayed preconditioning mimetic [39,40]. Hence nitroglycerin may also act to prevent ischemia 24–96 h after a single dose.
2.6. Can the pathologic heart be preconditioned?

A study by Ishihara et al. [41] suggested that diabetes prevented ischemic preconditioning in patients presenting with a first anterior wall myocardial infarction. They investigated 611 patients with a first anterior wall myocardial infarction—490 without diabetes and 121 with non-insulin treated diabetes who underwent emergency cardiac catheterization procedure. While in nondiabetic patients prodromal angina was associated with smaller myocardial infarct size as estimated by lower peak creatine kinase values, larger increase in left ventricular ejection fraction from admission to predischarge, and lower in-hospital mortality rates, in diabetic patients prodromal angina conferred none of these benefits. The authors postulated that there were a number of potential mechanisms for this observation: Ischemic preconditioning is mediated at least in part by activation of the $K_{\text{ATP}}$ channel and this channel may be altered in the diabetic heart [42]; hyperglycemia can abolish ischemic preconditioning [43]; and certain oral hypoglycemic drugs (such as glibenclamide) prevent ischemic preconditioning by blocking the $K_{\text{ATP}}$ channel [44,45]. Use of the sulfonylurea oral hypoglycemics has been associated with an increase in early mortality in diabetics following direct angioplasty for acute myocardial infarction [46]. While preconditioning appeared to be inhibited in diabetic patients, an experimental study by Tsang et al. [47] suggested that by increasing the ischemic preconditioning stimulus (increasing the number of ischemia/reperfusion cycles from one to three, which significantly phosphorylated AKT) the diabetic heart could be protected by preconditioning.

There has been controversy in the preclinical literature regarding the issue of whether hypercholesterolemic/atherosclerotic animals can be preconditioned [48]. Ueda et al. [49] observed that in a rabbit model of myocardial infarction that a high cholesterol diet abolished ischemic preconditioning; however, pravastatin at a dose that did not normalize serum cholesterol restored ischemic preconditioning. The authors postulated that pravastatin’s benefit was due to restoration of ischemic preconditioning-induced ecto-5’ nucleotidase activation.

In humans, it is well known that repetitive angioplasty balloon inflations can induce ischemic preconditioning. Kyriakides et al. [50] studied 33 patients undergoing a minimum of three balloon inflations as part of a coronary angioplasty procedure. Thirteen patients had a total cholesterol level of $<200$ mg/dL; and 20 had total cholesterol levels of $>200$ mg/dL. While in the normal cholesterol group, mean ST segment elevation on surface ECGs decreased from 0.21 mV during the first balloon inflation to 0.11 mV during a third inflation ($P<0.05$); in those patients with cholesterol levels of $>200$ mg/dL the decrease was from 0.18 to 0.14 MV ($P=\text{nonsignificant}$). Thus, in this study, hypercholesterolemia prevented the normal decrease in myocardial ischemia associated with angioplasty-induced preconditioning. Ungi et al. also recently observed that hypercholesterolemia attenuated the beneficial effects of preconditioning during coronary angioplasty [51].

Miki et al. [52] showed that in an experimental myocardial infarct model that ischemic preconditioning failed to protect myocardium that had been remodeled following a myocardial infarction and that an AT$_1$ receptor blockade with valsartan could preserve preconditioning.

Therefore, at least some studies in the literature suggest that certain pathologies (diabetes, hypercholesterolemia, remodeled left ventricle) may interfere with ischemic preconditioning but that certain therapies may restore preconditioning’s protection. As discussed under Section 2.2, there has been debate regarding whether preconditioning’s benefit is maintained or lost in the elderly heart.

3. Clinical application of preconditioning mimetics

Over the last 20 years there have been intensive investigations into the biochemical pathways that lead to the preconditioning phenomenon [5]. A number of pharmacologic agents are thought to act as triggers or effectors of ischemic preconditioning [5,53–56], including both the early phase of preconditioning as well as the late or delayed phase of ischemic preconditioning. Some of these agents that simulate ischemic preconditioning without inducing ischemia have been studied in humans and include adenosine, adenosine agonists, the $K_{\text{ATP}}$ channel/opener and nitrate-like agent nicorandil, delta opioids, volatile anesthetics, and nitroglycerin. It is important to realize that some of these agents may have protective benefits that are not directly related to ischemic preconditioning but involve other mechanisms. For example, adenosine might work through an antplatelet effect or an anti-inflammatory effect that is totally independent of preconditioning or postconditioning.

3.1. Cardiac surgery

3.1.1. Adenosine

Mentzer et al. reported studies on the use of adenosine as an additive to blood cardioplegia during coronary artery bypass surgery [57]. Sixty-one patients were randomized to receive either cold-blood cardioplegia alone or cold-blood cardioplegia with 1 of 5 adenosine doses (100 $\mu$M, 500 $\mu$M, 1 mM, 2 mM, and 2 mM plus a preischemic infusion of 140 $\mu$g/kg/min of adenosine). Ventricular function and rhythm were monitored preoperatively, prebypass and 1–24 h after bypass. Need for inotropic and vasoactive agents were recorded. Higher doses of adenosine were associated with less need for dopamine and nitroglycerin. In the placebo group the 24 h average dose of dopamine was 28-fold greater than in the high-dose adenosine patients, and use of nitroglycerin was 2.6-fold greater. Placebo and 100 $\mu$M adenosine had lower ejection fractions compared to patients receiving intermediate or high dose adenosine.
In a large double-blind, placebo-controlled, randomized trial [58] 253 patients undergoing coronary artery bypass surgery received either cold-blood cardioplegia, blood cardioplegia with 500 µM adenosine, or blood cardioplegia with 2 mM adenosine. Patients in the adenosine groups also received an infusion of 200 µg/kg/min of adenosine 10 min before and 15 min after removal of the aortic cross clamp. High dose adenosine adjunctive therapy resulted in a trend toward a decrease in need for high dose dobutamine (similar to the earlier trial), as well as a lower incidence of myocardial infarction. Patients receiving high-dose adenosine had a lower composite endpoint of high-dose dopamine use, use of epinephrine, need for intra-aortic balloon pump therapy, myocardial infarction, or death. The authors concluded that adenosine as an adjunct to cardioplegia was safe and yielded fewer postoperative complications [58,59].

Studies performed on human isolated right atrial trabeculae subjected to simulated ischemia showed that ischemic preconditioning and adenosine both improved developed force following ischemia/reperfusion and also preserved tissue CK activity [60]. KATP channel inhibition with glibenclamide eliminated the improvement in muscle function induced by either ischemic preconditioning or adenosine. Thus, adenosine may be a trigger for ischemic preconditioning in human tissue; the KATP channel may be a downstream end-effector.

Wasir et al. [61] also studied adenosine pretreatment in patients undergoing coronary artery bypass surgery. This was a small study of 20 patients with severe triple vessel disease and ejection fraction <35% who were randomized to adenosine pretreatment (200 µg/kg) prior to aortic cross-clamping versus saline infusion. The adenosine-treated patients demonstrated a higher cardiac output from 3.46 l/min to 4.46 l/min (P < 0.05) compared to the control group. Both systemic vascular resistance and pulmonary artery wedge pressure fell in the adenosine group. At 12 h postoperatively one patient in the adenosine group but 3 in the control group had an increase in creatine phosphokinase MB levels. The authors concluded that pretreatment with adenosine protected the heart during cardiopulmonary bypass including an improvement in postoperative hemodynamics.

Not all studies testing adenosine given prior to cardiopulmonary bypass have been positive. Belhomme et al. [62] administered a 5 min infusion of adenosine (140 µg/kg/min) into a central venous catheter followed by 10 min of washout prior to cardioplegic arrest (n = 23) or an equivalent period of pre-arrest drug-free control (n = 23) in patients undergoing coronary artery bypass surgery. Activity of ecto-S-5′-nucleotidase, a reporter of activation of the protein kinase C pathway – believed to be a crucial pathway in ischemic preconditioning – was measured from right atrial biopsies, and troponin I release over the first 48 postoperative hours was measured. Ecto-5′-nucleotidase levels were unchanged in control patients but increased with adenosine preconditioning. While this finding suggested that the protein kinase C pathway had been activated in patients, the postoperative values of the cardiac enzymes troponin I did not differ between control and adenosine groups, suggesting that adenosine preconditioning did not reduce ischemic necrosis associated with coronary artery bypass surgery.

Thus, while adenosine has shown benefit as an adjunct to cardioplegia in some studies, benefits have primarily suggested improved hemodynamics and less use of inotropic agents. Evidence that adenosine has truly reduced perioperative ischemic myocardial cell death is mixed. To our knowledge, adenosine is not routinely used by most cardiac surgeons.

3.1.2. Volatile anesthetics

Certain volatile anesthetic agents given transiently before prolonged ischemia could reduce myocardial infarct size to a degree comparable to ischemic preconditioning. One theory is that volatile anesthetics generate small amounts of reactive oxygen species that then trigger the preconditioning secondary messenger pathways [63,64]. Garcia et al. [65] studied the volatile anesthetic agent, sevoflurane, in 72 patients undergoing elective coronary artery bypass surgery. The patients were randomized to sevoflurane at 4 vol.% for 10 min versus placebo. Sevoflurane decreased the incidence of late adverse cardiac events (3%) versus placebo (17%, P = 0.038). New episodes of congestive heart failure occurred in one patient in the sevoflurane group versus three in the control group. Three patients in the control group developed coronary artery reoclusion. Perioperative peak concentrations of various markers of myocardial injury (cardiac troponin T, N-terminal pro-B-type natriuretic peptide) were higher in patients who developed late cardiac events. Sevoflurane reduced transcript levels for platelet–endothelial cell adhesion molecule and increased catalase levels measured from atrial biopsies.

De Hert et al. [66] also studied sevoflurane in 200 patients undergoing elective coronary surgery and compared its use in several regimens to the anesthetic propofol. Sevoflurane treatment reduced postoperative troponin I concentrations versus propofol. It also preserved stroke volume. Patients who received sevoflurane experienced shorter lengths-of-stay in the intensive care unit. The authors concluded that sevoflurane was cardioprotective in patients undergoing coronary artery bypass surgery and that the benefits were most apparent when it was administered throughout the procedure.

3.1.3. Nicorandil

Nicorandil is a KATP channel opener that also has nitrative properties. It is approved in several countries for the treatment of angina pectoris [67]. Some studies have now assessed its ability to pharmacologically precondition the heart undergoing surgery. Kawamura et al. [68] divided patients undergoing coronary artery bypass surgery to receive nicorandil (4–6 mg/h, n = 20) or no nicorandil (n = 20). Serum creatine kinase and troponin T levels increased 60 min after declamping the aorta, but these
parameters were lower in the nicorandil group than the control group. In vitro studies showed that nicorandil inhibited NF-Kappa-β, adhesion molecule expression, production of tumor necrosis factor-α, and inflammatory cytokines. The authors concluded that nicorandil protected the myocardium of patients undergoing cardiac surgery and that its mechanism was through inhibition of these deleterious humoral factors. In contrast, another study by Blanc et al. [69] administered nicorandil (10 mg twice a day, \( n = 22 \)) or placebo (\( n = 23 \)) to patients undergoing coronary artery bypass surgery. The effects of nicorandil on cardiac enzyme release and hemodynamics were neutral. The authors stated that nicorandil, as an antiangular agent, is safe to use up to premedication but was not cardioprotective. Larger studies are needed to clarify the role of this intriguing agent in coronary surgery.

### 3.2. Preconditioning mimetics for angioplasty

Repetitive brief angioplasty balloon inflations/deflations can induce ischemic preconditioning in humans resulting in less chest pain, less ST segment elevation, and less lactate production on subsequent compared to an initial balloon inflation. Studies have now shown that preconditioning mimetic agents, known to be involved in the second messenger biochemical pathway [5] of ischemic preconditioning, can also pharmacologically precondition the human heart. Hence agents such as adenosine [70] when given prior to coronary artery balloon inflation reduce electrocardiographic signs of ischemia and cause less chest pain, less deterioration of left ventricular ejection fraction, and less deterioration of isovolumetric phase indexes during angioplasty [71]. Leesar et al. [72] showed that adenosine given 10 min prior to three 2 min balloon inflations was associated with less systolic dysfunction assessed by 2-dimensional echocardiography, less diastolic dysfunction, and less lactate production on the first inflation compared to controls (no adenosine). The same group showed that bradykinin infusions could precondition the human heart when given prior to angioplasty as well [73].

Conversely, agents that block the preconditioning pathways appear to inhibit the beneficial preconditioning effects of repetitive balloon inflation/deflation sequences. The K\(_{\text{ATP}}\) channel blocker glibenclamide inhibited this type of preconditioning in humans [44]. Studies have also suggested that the opioid receptor may be important in inducing angioplasty inflation-induced preconditioning in humans. The opioid receptor antagonist naloxone given 15 min prior to angioplasty inhibited the benefits of repetitive balloon occlusion/reperfusion [74].

Recently, Leesar et al. demonstrated that certain pharmacologic agents, such as nitroglycerin, could induce a delayed preconditioning phenomenon in humans who were undergoing angioplasty [40]. They also showed that nitroglycerin could reduce exercise-induced ischemia when administered 24 h prior to ischemia [39].

While it is clear that pharmacologic preconditioning, like ischemic preconditioning, can protect human myocardium during angioplasty, this approach has not become standard clinical practice. Again, most interventionalists do not think that they need to protect the distal myocardium during brief balloon inflations and stent deployments. Nevertheless, either ischemic preconditioning or pharmacologic preconditioning remain options to interventionalists for high-risk patients, and high-risk coronary anatomies.

Some agents that have been shown to precondition the myocardium may have benefits on the no-reflow phenomenon or slow-reflow phenomenon associated with percutaneous coronary intervention. Thus nicorandil, when combined with adenosine for percutaneous coronary intervention in the setting of acute myocardial infarction, improved TIMI flow grade, TIMI frame count, myocardial blush score, and short term clinical outcome compared to adenosine alone [75].

Tsubokawa et al. [76] evaluated the effects of nicorandil on no-reflow/slow-reflow phenomenon during rotational atherectomy procedures. By angiography, no-reflow/slow-reflow phenomenon was observed in 17.4% of lesions in patients who received verapamil plus nitroglycerin versus 2.7% (\( P = 0.03 \)) who received nicorandil/nitroglycerin. Since these agents are being administered during ischemia and prior to reflow or with reflow, it is unlikely that nicorandil is working through a truly preconditioning mechanism. However, it is conceivable that it may be working through a postconditioning mechanism, as described below.

### 3.3. Preconditioning mimetics for angina/unstable angina

IONA (Impact of Nicorandil in Angina) was a randomized double-blind, placebo-controlled trial designed to test the hypothesis that nicorandil (target dose was 20 mg twice daily) could decrease cardiovascular events in patients with effort angina and cardiovascular risk factors [77]. These coronary artery disease patients were randomized to nicorandil [2565] versus placebo [2561] [78]. Primary outcome was coronary heart disease death, non-fatal myocardial infarction, and hospital admission for chest pain. Over a mean follow-up of 1.6 years, 15.5% primary endpoint events occurred in the placebo group versus 13.1% in the nicorandil group (\( P = 0.014 \)). Acute coronary syndromes occurred in 7.6% of the placebo group versus 6.1% of the nicorandil group (\( P = 0.028 \)). Rates for all cardiovascular events were lower in the nicorandil group (14.7%) versus the placebo group (17.0%, \( P = 0.027 \)). Thus nicorandil reduced major coronary events in patients with stable angina. Since this antiangular agent was given in a prophylactic fashion, it may be that at least part of its mechanism of action was related to pharmacologic preconditioning.

Preconditioning mimetics have also been administered to prevent exercise-induced ischemia. As mentioned, Jneid et al. [39] showed that intravenous nitroglycerin given 24 h prior to a planned exercise tolerance test could increase
exercise duration and decrease ST segment depression, suggesting that nitroglycerin served as a delayed preconditioning mimetic.

3.4. Preconditioning mimetics administered acutely to patients with myocardial infarction

Theoretically, a preconditioning mimetic agent would need to be administered prophylactically to high-risk patients prior to actual coronary artery occlusion in order to have a benefit. Yet, some preconditioning mimetic agents, including nicorandil and adenosine, appear to have benefit even when given after coronary artery occlusion and before or near the time of reperfusion. For example, nicorandil was shown to improve left ventricular function, reduce left ventricular remodeling, improve myocardial perfusion, and reduce cardiac events compared to percutaneous coronary intervention alone [79]. In one study by Ikeda et al. [80] nicorandil or isosorbide dinitrate was administered at admission for acute myocardial infarction and immediately after angioplasty. Nicorandil resulted in better recovery of ST segment elevation (55.5%) versus the isosorbide dinitrate group (19.2%, P = 0.006). Coronary artery peak velocity 40 min after reperfusion was better in the nicorandil group (13.3 cm/s) than the nitrate group (11.1 cm/s, P = 0.045) and regional wall motion in the infarcted area was improved 3 weeks after infarction in the nicorandil group compared to the nitrate group.

Nameki et al. [81] showed that when used as an adjunct to percutaneous coronary intervention for acute myocardial infarction, nicorandil given before reperfusion improved regional wall motion abnormalities, whereas magnesium did not. Ono et al. [82] showed that when combined with primary percutaneous coronary intervention for acute myocardial infarction, nicorandil improved cardiac function, reduced no-reflow, and was associated with a lower brain natriuretic peptide at 6 months compared to controls. Ueda et al. [83] showed that nicorandil decreased the incidence of QT dispersion and ventricular fibrillation in patients with successful coronary angioplasty for acute myocardial infarction. Kasama et al. [84] showed that nicorandil has benefits on the cardiac sympathetic nerves, as well as remodeling in the setting of first anterior myocardial infarction.

Other clinical studies have shown benefits of nicorandil in patients with acute myocardial infarction [85,86]. In addition, the Japan-Working groups of acute myocardial Infarction for the reduction of Necrotic Damage by a KATP channel opener (J-WIND-KATP) have begun a large prospective, randomized, multicenter trial to determine whether nicorandil reduces myocardial infarct size and improves regional ventricular wall motion [87]. Patients with acute myocardial infarctions who are candidates for percutaneous coronary intervention will be randomized to placebo versus nicorandil with the primary endpoint being infarct size and left ventricular function. This study is ongoing. Certainly, the studies regarding nicorandil’s beneficial effect in the setting of percutaneous coronary intervention for acute myocardial infarction must involve mechanisms other than ischemic preconditioning given the timing of administration of the drug. It is possible that nicorandil may postcondition the myocardium or perhaps its vasodilating properties, by reducing no-reflow or slow-reflow, may enhance reperfusion, or as described above its benefit may be related to a salutary effect on the sympathetic nervous system.

Another preconditioning mimetic that has shown promise in the setting of acute myocardial infarction is adenosine, even though its mechanism may have little to do with preconditioning. Several small studies suggested that adenosine given to patients undergoing coronary reperfusion therapy for acute myocardial infarction resulted in smaller infarct sizes and/or other clinical benefits [88–92]. In the AMISTAD-II (Acute Myocardial Infarction STudy of ADenosine) study [93] 2118 patients with evolving anterior wall ST segment elevation myocardial infarction and receiving either thrombolytic therapy or primary angioplasty were randomized to a 3 h infusion of adenosine 50 μg/kg/min, 70 μg/kg/min, or placebo. Study drug had to be started within 15 min either of the start of thrombolytic therapy or prior to coronary intervention. The primary endpoint of death or new congestive heart failure occurred in 17.9% of the placebo patients and 16.3% of the pooled adenosine patients (P = NS). A myocardial infarct size substudy utilizing technetium-99 m sestamibi tomography revealed that high dose adenosine reduced myocardial infarct size (11% of the left ventricle) versus placebo (27% of the left ventricle, P = 0.023).

Again, since adenosine was given during ischemia and not in a pretreatment fashion, it is unlikely that its beneficial effects observed on myocardial infarct size were related to preconditioning. It may have been related to postconditioning, an anti-inflammatory effect, a reduction in apoptosis, or an antiplatelet effect whereby adenosine helped to keep the infarct-related artery open.

4. Postconditioning

As recently described and reviewed by Jakob Vinten-Johansen, “postconditioning is a series of brief mechanical interruptions of reperfusion following a specific prescribed algorithm applied at the very onset of reperfusion” [94]. Zhao et al., and Halkos et al. [95,96] showed that interrupting reperfusion following a 1 h coronary artery occlusion in the canine model (with an algorithm of 30 s reperfusion followed by 30 s of reocclusion repeated 3 times) followed by full reperfusion for 3 h could reduce myocardial infarct size to a level equivalent to ischemic preconditioning. This cardioprotective effect was associated with an improvement in endothelial function, a reduction in tissue superoxide generation, a reduction in cardiac apoptosis, and a decrease in microvascular injury [94]. Adenosine was implicated as adenosine blockers could inhibit the benefit. Other mecha-
nisms that have been implicated in the postconditioning phenomenon are epithelial nitric oxide synthase, nitric oxide and guanylyl cyclase, the K(ATP) channel, and closing of the mitochondrial permeability transition pore [94]. Postconditioning, theoretically, might be more clinically applicable than preconditioning in that therapy would not have to be administered prior to an ischemic episode, but could be administered at the time of reperfusion. It should be noted that at the present time postconditioning for reducing myocardial infarct size has not been observed in all species tested, including the pig model. It has been reported to occur in dogs, rabbits, mice, and rats [94].

There are a few studies that examined whether postconditioning can occur in humans. Laskey [97] reported a study of 17 patients undergoing percutaneous coronary intervention for acute myocardial infarction who were randomly assigned to standard reperfusion therapy or what the author called a preconditioning protocol (although in the strict sense of the definition it was postconditioning, since reperfusion by balloon angioplasty had already occurred at the time of his protocol). The postconditioning protocol consisted of two 90 s balloon inflations with 3–5 min of reperfusion between them.

Final ST segment elevation in the postconditioning group (1.60 mV) was less than in the control group (4.0 mV, P<0.001). The rate of ST segment resolution was more rapid in the postconditioning group and coronary flow velocity reserve was also improved. The author concluded that brief periods of coronary occlusion and reperfusion during percutaneous coronary intervention for acute myocardial infarction reduce ischemic injury and improve distal perfusion of the myocardium. The results of this study were intriguing, but a larger study was needed to assess this approach for actually reducing myocardial infarct size or improving clinical outcomes in patients. One theoretical concern was that multiple balloon inflations and deflations in the coronary arteries of humans could embolize atherosclerotic debris into the distal coronary arteries. However, this apparently was not a problem in Laskey’s study where distal perfusion was improved by this maneuver [97].

Staat et al. [98] recently published a pioneering study in which 30 patients admitted for coronary angioplasty for acute myocardial infarction were assigned to reperfusion with direct stenting alone (control group) or were subjected to a postconditioning protocol following reperfusion by stenting. The postconditioning protocol consisted of one minute of reflow followed by one minute of angioplasty balloon inflation and one minute of balloon deflation times four. The area at risk was determined from a left ventricular angiogram. The two groups were equally matched for area at risk, collateral flow assessed by coronary angiography, and duration of ischemia. However myocardial infarct size, estimated by the area under the curve of creatinine kinase release, was 36% lower in the postconditioned group. Blush grade, a marker of microvascular patency following reperfusion, was also better in the postconditioned group. This is an important study in that it is the first carefully performed, systematic approach to postconditioning patients with a coronary angioplasty balloon that demonstrates that postconditioning may reduce myocardial infarct size in patients with equally matched risk zones.

Postconditioning could be applied to interventional techniques during reperfusion for acute myocardial infarction, but also for interventions being performed in patients with stable or unstable angina. Again, however, just as ischemic preconditioning as a therapy never caught on among interventionalists, the use of stents and drug eluting stents will make routine use of postconditioning protocols for interventions performed outside the setting of acute myocardial infarction unlikely.

As noted above, both adenosine and nicorandil have shown promise in the setting of reperfusion for acute myocardial infarction. Since adenosine and the K(ATP) channel have been implicated in the mechanism(s) of postconditioning in animal models, it is theoretically possible that the clinical benefits of nicorandil and adenosine in the setting of reperfusion for acute myocardial infarction in humans are their first examples of the clinical use of postconditioning mimetic drugs.

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