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Editorial

Clinical Application of Remote Ischemic Preconditioning

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Ischemic preconditioning[1] has been shown to reliably reduce ischemic myocardial cell necrosis in a host of animal models.[2] Although preconditioning is one of the most powerful and reproducible phenomena in cardioprotection, it has not readily translated to routine clinical use. One issue is that the timing of the long duration of ischemia must be known in advance and the treatment must be applied before the long duration of ischemia. Thus, although evidence suggests that preinfarction ischemia (angina) before an ST-segment elevation myocardial infarction is associated with smaller infarct size and better clinical outcome,[3] there is no reliable way to predict when a myocardial infarction will occur and hence no way to either induce ischemic preconditioning or apply a preconditioning mimetic agent just before the infarction. There are, of course, situations in which myocardial ischemia is planned, eg, during coronary artery balloon angioplasty, during coronary artery bypass surgery, during excision and transportation of a donor heart, and before exercise in a patient with known demand-induced ischemia. Preconditioning has been applied to some of these situations. For example, multiple brief balloon inflations and deflations in the coronary artery reduce the severity of chest pain, ST-segment elevation, and lactate production on subsequent balloon inflations compared with an initial balloon inflation without necessarily recruiting blood flow.[4] Intermittent aortic cross clamping before coronary artery bypass surgery has been observed to preserve cardiac high-energy phosphate levels.[2] These examples of ischemic preconditioning require an invasive procedure to induce ischemia within the heart and the possibility of showering atherosclerotic emboli either down the coronaries or into the aorta as a coronary angioplasty balloon is repeatedly inflated or deflated or the aortic cross clamp is repeatedly clamped and unclamped.

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Another approach exists that has the potential to be entirely noninvasive: remote ischemic preconditioning (also called ischemic preconditioning at a distance). The initial study suggesting that 1 vascular bed could precondition another vascular bed came from Przyklenk et al[5] in 1993. Using anesthetized dogs, we showed that 4 episodes of 5 minutes of circumflex coronary artery occlusion interspersed with 5 minutes of reperfusion before a 1-hour sustained left anterior descending coronary artery occlusion plus 4.5 hours of reperfusion markedly reduced the size of the myocardial infarction in the left anterior descending bed (6±2% of the risk zone) compared with nonpreconditioned controls (16±5% of the risk zone; $P<0.05$). In addition, segment shortening of the left anterior descending region was improved by preconditioning the circumflex bed, reflecting the smaller infarct size. Preconditioning the circumflex coronary artery bed did not affect collateral flow within the left anterior descending coronary bed. Przyklenk et al showed that the magnitude of infarct size reduction (35%) by preconditioning the opposite coronary bed was similar to that of standard preconditioning within the same coronary bed.

This basic concept was followed by additional studies suggesting that ischemia of remote organs such as the kidney or mesentery could confer protection to the ischemic myocardium. In 1997, Birnbaum et al[6] published the first study suggesting that transient limb ischemia could remotely precondition the ischemic heart. In that study, anesthetized rabbits were subjected to 30 minutes of coronary artery occlusion and 4 hours of reperfusion. Before this long coronary artery occlusion, rabbits were randomized to a 30-minute waiting period (control group), stenosis of the femoral artery to reduce femoral artery blood flow by 55% to 65%, rapid electric stimulation of the gastrocnemius muscle, or a combination of femoral artery stenosis plus rapid electric stimulation of the gastrocnemius muscle. Myocardial infarct size, expressed as a percentage of the risk zone, was 26% in controls, 36% in the femoral stenosis group, and 30% in the muscle stimulation group but reduced to 9% in the femoral stenosis plus stimulation group ($P=0.0006$). Regional myocardial blood flow measurements revealed that all groups had equal degrees of myocardial ischemia during coronary artery occlusion. Gastrocnemius muscle stimulation plus femoral artery stenosis also reduced infarct size in rabbits undergoing atrial pacing. Thus, the authors showed that by altering the oxygen supply-demand balance in remote skeletal muscle, myocardial protection was achieved.[6] Subsequently, transient limb ischemia in humans was shown to protect against endothelial ischemic reperfusion injury of an opposite limb[7] and to reduce ischemic myocardial damage during coronary artery bypass surgery[8] and pediatric cardiac surgery.[9]

The Present Study

In this issue of *Circulation*, Hoole et al[10] extend the concept of remote ischemic preconditioning to show that transient limb ischemia (three 5-minute blood pressure cuff inflations to 200 mm Hg around the upper arm followed by 5 minutes of reperfusion) before arrival in the catheterization laboratory for percutaneous coronary intervention (stenting) signifi-

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cantly decreased median troponin I concentrations at 24 hours (0.06 ng/mL) compared with nonpreconditioned patients (0.16 ng/mL; $P=0.04$). Remote ischemic preconditioning was associated with less chest pain and fewer ischemic ECG abnormalities during percutaneous coronary intervention. At 6 months, there were fewer major adverse cardiac events in the remote ischemic preconditioning group compared with control subjects (4 versus 13; hazard ratio, 0.28; $P=0.018$).

The present study was performed as a prospective, randomized controlled trial that included 242 consecutive patients at a single center. It appears to be a carefully performed study that adds important new knowledge to the field of ischemic preconditioning. The data add to the growing number of studies suggesting that remote ischemic preconditioning is a safe, effective, noninvasive, and cost-effective strategy for reducing ischemic cardiac damage in settings where myocardial ischemic damage is expected. One might argue whether there is any real advantage of remote ischemic preconditioning involving a limb compared with repetitive percutaneous coronary angioplasty balloon inflation and deflation to condition the ischemic myocardial bed in the setting of percutaneous coronary intervention. Repetitive balloon inflation and deflation, although shown to be effective, could potentially contribute to showering the distal myocardium with emboli of atherosclerotic and thrombotic debris. Furthermore, repetitive trauma to the underlying vessel might worsen endothelial dysfunction and contribute to restenosis. Transient limb ischemia was shown in the present study to have no adverse effects. The approach of inducing preconditioning by inflating a blood pressure cuff to transiently occlude the brachial artery is noninvasive and technically easy. It requires no expensive medicines or equipment—only a blood pressure cuff and trained healthcare professionals.

Remote ischemic preconditioning by blood pressure cuff inflation of a limb can also be applied to other situations in which myocardial ischemia is expected besides planned percutaneous intervention, as shown by recent cardiac surgical studies using similar techniques before coronary artery bypass surgery and pediatric cardiac surgery.

Examples of the Clinical Utility of Remote Ischemic Preconditioning for Cardiac/Vascular Surgery

Hausenloy et al[8] studied 57 patients who underwent coronary artery bypass surgery. Patients were randomized to either control (n=30) or remote ischemic preconditioning (n=27) induced by three 5-minute episodes of right upper limb ischemia (with an automated blood pressure cuff inflated to 200 mm Hg) and by 5 minutes of cuff deflation (reperfusion) after induction of anesthesia. Serum troponin T concentration was measured before surgery and 6 to 72 hours after surgery. Remote ischemic preconditioning decreased the total area under the curve of serum troponin T from 36 μg/L in control subjects to 21 μg/L in the remote ischemic preconditioning group (a 43% reduction; $P=0.005$). Thus, remote ischemic preconditioning using transient upper arm ischemia reduced ischemic myocardial damage during elective coronary artery bypass grafting.

Kharbanda et al[7] studied the effect of remote ischemic preconditioning on endothelial ischemia/reperfusion injury. Endothelial ischemia/reperfusion injury was induced by 20 minutes of upper limb ischemia by inflating a blood pressure cuff to 200 mm Hg followed by deflation (reperfusion). The therapy, remote ischemic preconditioning, was created by inducing three 5-minute periods of upper limb ischemia to the contralateral limb. Forearm blood flow was determined with venous occlusion plethysmography in response to acetylcholine both at baseline and 15 minutes after reperfusion. The vasodilating response to acetylcholine was attenuated in control patients after 15 minutes of ischemia and 20 minutes of reperfusion. Remote ischemic preconditioning of the contralateral limb prevented the attenuation of the vasodilating effect of acetylcholine. Kharbanda et al also showed that four 5-minute cycles of ischemia in the lower limbs of pigs reduced the size of an experimentally induced myocardial infarct. Of note, the K_{ATP} channel blocker glibenclamide was recently shown to block the benefit of remote ischemic preconditioning, suggesting that protection is dependent on K_{ATP} channel activation.[11]

Ali et al[12] determined whether remote ischemic preconditioning could reduce both myocardial and renal injury in patients undergoing major vascular surgery, specifically open abdominal aortic aneurysm repair. They randomized 82 patients undergoing abdominal aortic aneurysm repair to remote ischemic preconditioning or to conventional repair. In their study, remote ischemic preconditioning was induced by 2 episodes of intermittent cross clamping of the common iliac artery with 10 minutes of ischemia followed by 10 minutes of reperfusion. Remote preconditioning reduced the incidence of myocardial injury by 27% (assessed by troponin I level >0.4 ng/mL), reduced the incidence of myocardial infarction by 22%, and decreased renal impairment by 23% (all 3 statistically significant). Multivariate analysis showed that the beneficial effect of remote ischemic preconditioning on all 3 of these parameters was independent of other covariables.

Cheung et al[9] reported a randomized controlled trial assessing the effects of remote ischemic preconditioning on children having cardiac surgery. Pediatric patients (n=37) undergoing cardiac surgery for repair of congenital heart defects were randomized to four 5-minute cycles of lower limb ischemia induced by inflating and deflating a blood pressure cuff or to control (no remote ischemic preconditioning). The primary measures were troponin I and lung mechanics carried out both preoperatively and postoperatively. The average age of the patients was 0.9 to 2.2 years. Troponin I levels were lower in the remote ischemic preconditioning group than the control group. Postoperative inotropic requirements were lower in the preconditioned patients than control subjects; the treated patients also demonstrated lower airway resistance than control subjects.

Thus, there are already quite a few studies in the surgical literature that support the concept that remote ischemic preconditioning can be used to reduce myocardial ischemic damage.

In addition, remote ischemic preconditioning might benefit hearts being harvested for transplantation or perhaps patients with unstable angina (the Table). It is possible that patients with unstable angina who receive remote ischemic preconditioning might be less likely to progress to myocardial infarction.

Table. Potential Clinical Uses of Remote Ischemic Preconditioning

Reducing cardiac damage during PCI
Protecting the myocardium during CABG and other cardiac surgical procedures requiring cardiopulmonary bypass
Protecting the vasculature during vascular surgery procedures
Unstable angina
Before activities that reproducibly cause angina in patients with stable angina
Protecting donor hearts before excision and transport
Protecting other organs (brain, kidney) during episodes of ischemia

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft.

Another possibility is that remote ischemic preconditioning could be induced in angina patients who consistently develop angina with certain activities (exercise, sexual activity). Is it possible that remote ischemic preconditioning might be applied to protect other organs besides the heart? Perhaps this type of therapy might benefit patients experiencing ischemia in other organs such as the brain, kidney, or gut.

The Mechanism of Remote Ischemic Preconditioning

The mechanism of remote ischemic preconditioning remains unknown. Theories include the concept that humoral substance(s) such as adenosine or bradykinin are produced by preconditioning, are released into the systemic circulation, and then protect the remote region or organ.[6,13] Other mechanistic factors proposed include erythropoietin, activation of the K_{ATP} channel,[14,15] nitric oxide,[16] delta 1-opioid,[17,18] and free radicals.[17]

Another theory is that ischemic preconditioning of 1 region or organ induces a generalized catecholamine stimulation or a sympathomimetic nerve stimulation that then induces cardioprotection. Some studies have suggested that certain catecholamines can mimic the benefit of ischemic preconditioning.[6] Gho et al[19] reported that the ganglion blocker hexamethonium abolished the benefit on the heart of remote ischemic preconditioning–induced mesenteric artery occlusion, supporting the involvement of a neurogenic pathway. Other studies also have favored a neurogenic pathway.[20]

Although the exact mechanism for remote ischemic preconditioning is not yet known, additional rigorous clinical trials using this safe and noninvasive technique are warranted. Sadly, funding for studies involving blood pressure cuff inflation will be difficult to obtain, given the fact that no new pharmacological agent or device is required. Nevertheless, there are few noninvasive therapies that can effectively reduce the amount of ischemic myocardial necrosis, and repetitive brachial artery occlusion and reperfusion with a blood pressure cuff appears to be one of them.

Disclosures

None.

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