

# Ischemic Preconditioning for the Clinician

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## ABSTRACT

Ischemic preconditioning is a physiologic phenomenon that occurs in the cardiac muscle in which brief episodes of ischemia protect the heart when exposed to a sustained ischemia. Clinical counterparts include potential benefits of preinfarction angina and less ischemia after a second, compared to a first, coronary angioplasty balloon inflation. This article will discuss how preconditioning might be applied to the clinical setting during acute myocardial infarction, coronary interventions, and cardiac surgery.

## INTRODUCTION

One of the most important moments in the life of a cardiac patient is the moment of reperfusion following a period of myocardial ischemia. Whether reperfusion is accomplished by thrombolytic therapy, acute coronary intervention, or by releasing the clamp at the end of a bypass surgery, the time from beginning of ischemia to reperfusion is of the essence. The sooner the blood flows into a coronary bed, the more myocardial salvage is achieved.<sup>1</sup>

At the exact moment of reperfusion, the clinician's main goal is cardiac protection.<sup>2</sup> Many cardiac phenomena impact on myocardial salvage and protection, some with a positive impact such as preconditioning,<sup>3</sup> and others with a negative impact such as reperfusion injury,<sup>4,5</sup> myocardial stunning,<sup>6</sup> and no-reflow.<sup>7,8</sup> All these phenomena interact (Figure 1). In this article, ischemic

preconditioning will be discussed in relationship to potential therapies in the clinical setting. Preconditioning refers to the phenomenon whereby brief episodes of ischemia prior to a longer severe episode of ischemia reduces myocardial infarct size.

## OVERVIEW

### *Before the Storm*

Preinfarction angina may be a clinical correlate of ischemic preconditioning. Preinfarction angina protects human myocardium and results in a smaller infarct size.<sup>9,10</sup> While inquiring about anginal history in patients presenting with acute myocardial infarction may offer prognostic value, it will have no strategic significance. Patients simply do not know when they will have their cardiac event. Is there any intervention that can offer the protection of ischemic preconditioning to the patients?

Regular exercise was shown to offer a benefit similar to that of preinfarction angina. Furthermore, it preserves ischemic preconditioning in the elderly.<sup>3</sup> Thus, in addition to the well-established benefits of exercise, enhancing cardiac conditioning is yet another reason to stay physically active. On the contrary, hyperglycemia<sup>11</sup> and some drugs, such as cyclooxygenase (COX)-2 inhibitors<sup>12</sup> and sulfonylureas,<sup>13</sup> may impair preconditioning. Staying physically active and avoiding such drugs may help cardiac patients in the event that they sustain a myocardial infarction.

### *Preconditioning and Thrombolytic Therapy*

Thrombolytic therapy is effective for acute myocardial infarction, and early reperfusion protects the heart.<sup>14</sup> Preinfarction angina has been shown to further protect patients receiving thrombolytic therapy for acute myocardial infarction. Preinfarction angina resulted in smaller infarction size,<sup>9,10</sup> improved cardiac function, and fewer cardiac arrhythmias.<sup>15-19</sup> Some pharmacologic agents stimulate the biochemical pathway

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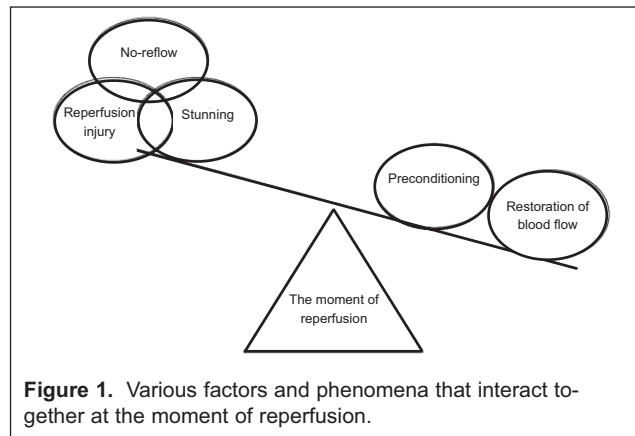
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of ischemic preconditioning without causing ischemia. Such agents are referred to as preconditioning mimetic drugs. Only a handful of preconditioning mimetic drugs have been successful in the setting of reperfusion therapy. Parenteral nitroglycerin was studied in a conscious rabbit model of infarction. It had a benefit that was equivalent to ischemic preconditioning.<sup>20</sup> No recent nitroglycerin trial is available in humans with regard to preconditioning and thrombolytic therapy. The preconditioning mimetic that was studied most extensively in clinical trials is adenosine.<sup>21-23</sup> Despite strong basic scientific evidence for the use of adenosine in acute myocardial infarction, the major controlled clinical study—the Acute Myocardial Infarction Study Adenosine (AMISTAD)-II—was disappointing, as adenosine fell short of the hoped clinical benefit, with only a small nonsignificant trend toward reduction of congestive heart failure and death.<sup>24</sup> However, in AMISTAD I and AMISTAD II, adenosine did—at high dose—reduce the size of acute anterior myocardial infarctions. There is a need for larger studies investigating adenosine and other preconditioning mimetic drugs in the setting of thrombolytic therapy.<sup>25</sup>

#### *Preconditioning in the Interventional Suite*

The benefit of preconditioning on ischemia was known in the early days of angioplasty, a few years before the term preconditioning was even described. Ischemic changes as measured by chest pain score, ST segment depression, and lactate production were more marked during the first intracoronary angioplasty balloon inflation as compared to subsequent inflations. No clear mechanism was known, and it was initially speculated that the benefit was related to collateral recruitment. However, it is now known that ischemic preconditioning is the predominant mechanism.<sup>26</sup> An antiarrhythmic effect of preconditioning also is well documented during angioplasty. One hundred fifty-six patients underwent 2 identical balloon occlusions separated by a 5-minute period and the incidence of ventricular ectopy was significantly less during the second inflation.<sup>27</sup>

An important study done by Laskey and Beach investigated the clinical significance of ischemic preconditioning in patients with coronary artery disease.<sup>28</sup> Three hundred eighty-two patients underwent elective balloon inflation for 90 seconds, to be repeated exactly in the same fashion after 5 minutes of normal perfusion. The degree of cardiac ischemia was measured by the degree of ST segment shift at the end of inflation. The degree of ischemia during the second inflation was less than the first, suggesting a preconditioning effect. Individual



**Figure 1.** Various factors and phenomena that interact together at the moment of reperfusion.

patients showed a different degree of protection from ischemic preconditioning. Some patients, usually diabetic and elderly patients, obtained little or no protection. In-hospital ischemic events were more likely to occur in those patients who did not experience ischemic preconditioning. Thus, ischemic preconditioning can provide prognostic information in that hearts that can adapt to an initial ischemic insult are more likely to be able to withstand future ischemic events.

The contemporary interventional cardiology laboratory rarely has need to precondition a coronary bed prior to an intervention. In the stent era, acute occlusion from a coronary dissection is now uncommon. Most angioplasty procedures do not require prolonged inflation. Hence, ischemic preconditioning by multiple balloon inflations is rarely used as a needed therapy in the interventional suite.<sup>26</sup>

#### *Preconditioning Mimetics During Intervention*

Some pharmacologic preconditioning agents do reduce the degree of ischemia similar to a prior balloon occlusion. Doorey et al published the benefit of intracoronary injection of nitroglycerin prior to balloon inflation.<sup>29</sup> Several mechanisms were suggested, but the authors did not include preconditioning since the term had yet to be coined. More recently, Leeser et al showed that the benefit of nitroglycerin given prior to angioplasty is mainly due to ischemic preconditioning. In an elegant study, they proved that nitroglycerin will induce a delayed preconditioning effect, meaning that its effect will have a benefit even a day or more after administration of the drug.<sup>30</sup> Similarly, adenosine and adenosine agonists will induce preconditioning and thus make adenosine a potentially important agent, especially in acute coronary syndromes.<sup>31,32</sup> Adenosine has a preconditioning-like effect, as well as a beneficial effect on the management of coronary no-reflow.<sup>33</sup> Nicorandil appears to be another very promising drug. Nicorandil is a hybrid be-

tween nitrate and a potassiumATP channel-opener.<sup>34</sup> When it is used in combination with acute intervention for myocardial infarction, it leads to reduced left ventricular remodeling with improved ventricular function,<sup>35</sup> and may reduce the occurrence of ventricular arrhythmias.<sup>36</sup> Of note, some investigators believe that the K-ATP channel is the end-effector for the benefit of ischemic preconditioning, perhaps making nicorandil the ultimate preconditioning mimetic. In small studies, nicorandil was compared to nitrates,<sup>37</sup> intravenous magnesium,<sup>38</sup> and intracoronary adenosine,<sup>39</sup> and appeared to be superior. In a recent study, 58 patients with acute myocardial infarction undergoing acute coronary intervention were randomized to nicorandil as a 4 mg bolus injection followed by 8 mg per hour for 24 hours or placebo. The nicorandil group developed fewer in-hospital cardiac events and demonstrated a decreased incidence of target vessel revascularization.<sup>40</sup> The drug's benefit appears to be improving coronary flow, as well as inducing preconditioning. Among various preconditioning mimetic drugs, nicorandil appears to be one of the most promising because of its effectiveness, and the fact that it also can be used intravenously, extending its benefit to the coronary care units. A new, large multicenter study using this agent was launched in Japan,<sup>41</sup> but results of the study are not yet available. The drug is not yet commercially available in the United States.

#### *Preconditioning and Coronary Bypass Surgery*

During coronary artery bypass surgery, despite the various surgical protocols for cardiac protection, the cardiac muscle invariably suffers some degree of ischemic injury, often a functional injury manifest by post-operative left ventricular dysfunction, but sometimes by perioperative infarction. This is the case whether the "on pump" traditional technique utilizing cardiac arrest and cardiopulmonary bypass, or the emerging "off pump" technique is used. In high-risk populations of acute coronary syndromes, mortality rates of up to 3.7% and perioperative infarction of about 10% were reported.<sup>42</sup> There is a need then for better cardiac protection during cardiac surgery. Preconditioning that was proven to provide a benefit during percutaneous coronary intervention may be even more beneficial during the prolonged strain throughout coronary artery bypass surgery.

*On Pump Bypass Surgery*—As early as 1993, Yellon et al introduced the concept of cardiac preconditioning during cardiac surgery.<sup>43</sup> Fourteen patients undergoing bypass surgery were randomized to the ischemic preconditioning protocol or the usual technique.

Preconditioning was performed with 2 3-minute periods of aortic cross clamping separated by 2 minutes of reperfusion. Higher tissue adenosine triphosphate levels were observed in the preconditioning group as compared to the control group. Utilizing similar protocols, substantial clinical benefits were shown. In a controlled study, ischemic preconditioning was associated with a higher cardiac index after surgery.<sup>44</sup> Improvement of function was also shown in the right ventricle.<sup>45</sup> In a separate study of 86 bypass patients who were randomized to ischemic preconditioning or control, the preconditioning group had less ventricular arrhythmias at reperfusion and during the first 24 hours after surgery.<sup>46</sup> As seen in some clinical studies, the benefit of preconditioning seems to decline with age.<sup>47</sup>

Despite the well-recognized benefits of the repeated cross clamp technique, it is not routinely used during cardiac surgery. The additional time it adds to the surgical procedure and the added risk of possible aortic embolic events restricted its popularity. Some surgeons rely on the choice of specific anesthetic agents that may act as preconditioning mimetics,<sup>48-50</sup> while others are experimenting with additional preconditioning mimetic drugs.<sup>51,52</sup> An effective, easy-to-use protocol needs to be developed to take better advantage of this phenomenon during on-pump bypass surgery.

*The Off-Pump Technique*—With this technique, the bypass is done on a moving heart, performing individual anastomosis using coronary immobilizers. If brief episodes of ischemia were induced prior to clamping the coronary artery to perform the anastomoses, they likely would confer protection similar to the initial animal studies of ischemic preconditioning. This technique, however, is not routinely utilized at the present time. Preconditioning mimetics, particularly adenosine, were utilized with some success.<sup>53</sup>

#### *Cardiac Transplantation*

Despite the current preservation techniques, the harvested donor heart may show some stunning (post-ischemic left ventricular dysfunction) effect or other stigmata of cardiac ischemia. Ischemic preconditioning improved ischemic preservation in sheep and rat<sup>54</sup> models of transplantation. Furthermore, nicorandil appears to be a preconditioning mimetic in the rat model<sup>54</sup> and should stimulate interest for the drug to be studied in humans during transplantation, as well as other cardiac surgeries.

#### *Ischemic Post-Conditioning*

Ischemic post-conditioning refers to brief periods of ischemia in the early period of reperfusion that reduce

myocardial infarct size. Ischemic post-conditioning was shown to occur in more than 1 animal model.<sup>55</sup> Few studies are available in humans. In a pilot study that involved only a handful of patients, Laskey has shown that ischemic post-conditioning may enhance successful reperfusion in humans.<sup>56</sup>

A very recent study by Staat et al<sup>57</sup> studied 30 patients who received stenting for acute myocardial infarction. Patients were randomized to control or post-conditioning, whereby they had 1 minute of reflow and then 4 episodes of 1 minute balloon inflation and 1 minute balloon deflation. Myocardial infarct size, assessed by measuring total creatine kinase release was reduced by 36% in the post-conditioning group. In addition, blush grade, a marker of successful microvascular reperfusion, was improved in the post-conditioning group. These 2 studies pave the way for possible larger clinical trials on post-conditioning in humans. The phenomenon of post-conditioning may be more practical than preconditioning (since it can be administered after reperfusion) and has significant potential, particularly during acute intervention in acute myocardial infarction and during coronary artery bypass surgery.

## CONCLUSION

Ischemic preconditioning is nature's contribution to protecting the heart during ischemic insults. The benefit was demonstrated in the coronary care unit in patients who had preinfarction angina prior to their acute myocardial infarction, in the interventional suite during acute percutaneous coronary intervention, and in the operating room during cardiac surgery. Despite a variety of protocols to induce the preconditioning effects, preconditioning mimetic drugs appear to offer the best hope for clinical utility. Adenosine and nicorandil in particular carry the highest potential for success since they can be administered intravenously, have shown promise in some studies, and are currently undergoing intense investigation. More work is needed to not only discover the ideal drug for clinical use, but also to familiarize clinicians about this important phenomenon of preconditioning.

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