brief episode of myocardial ischemia confers endogenous cardioprotection during a subsequent prolonged period of ischemia. This phenomenon, known as preconditioning, offers one of the most powerful mechanisms for reducing the speed and extent of myocardial cell damage resulting from an acute or sustained ischemic insult. This protection has been shown to occur in a wide variety of animal species, including man, and exists in two forms, namely an early or classic preconditioning and delayed or second window of protection. The "gold standard" used in these animal studies for assessing a preconditioning effect has been measurement of the extent of limitation of infarct size. Studies in humans therefore necessarily rely on a less direct approach. For example, clinical observation has shown that the occurrence of episodes of angina shortly before a myocardial infarction reduces mortality and morbidity. In the setting of percutaneous transluminal coronary angiography, it has been shown that measures of ischemia, such as angina and ST elevation, in the ECG occurring during the period when the coronary artery is occluded by the inflated balloon are less during a second balloon inflation compared with the first. These studies are not always easy to interpret, however, because of confounding variables such as uncertainties about the recruitment of collaterals in response to the preconditioning ischemia, the adequacy of the very short duration of ischemia sometimes used during the preconditioning phase, and the use of the amount of ST segment shift in the ECG as a quantitative measure of ischemia. One study largely overcomes the uncertainties with regard to collateral flow in patients undergoing percutaneous transluminal coronary angiography and demonstrates an antiarrhythmic effect of preconditioning. Possibly the most direct evidence for the occurrence of preconditioning in humans comes from studies in patients undergoing coronary artery surgery, where it has been shown that the introduction of two 3-minute periods of global ischemia early in the operation reduced the loss of high energy phosphates and troponin T after the subsequent prolonged period of ischemia during the fashioning of the coronary graft anastomoses. Thus, overall, the available evidence supports the notion that preconditioning not only occurs in humans but does so within context of clinical procedures and as such may be of potential benefit to patients.

While preconditioning has been shown to dramatically reduce infarct size in all species studied, the situation with regard to surrogate endpoints such as ventricular arrhythmias is less clear. The majority of studies in animal models report a reduction in arrhythmias after preconditioning protocols. Some studies, on the other hand, report a worsening of arrhythmias. For example, in the original study by Murray et al, there was a trend to an increased susceptibility to ventricular fibrillation (VF) in preconditioned dogs. In another study, although preconditioning reduced infarct size in pigs, it also accelerated the time to VF. Notable in this regard is the general lack of information regarding preconditioning in humans. This is rectified in the current issue of Circulation by the article by Wu and colleagues, who report a study in humans in which they examined the effect of a preconditioning protocol on perioperative and postoperative arrhythmias. They studied 86 patients undergoing coronary artery bypass surgery. Half of the patients received a preconditioning protocol early in the operative procedure consisting of two 2-minute periods of global ischemia before the longer period of ischemia that accompanied the graft procedures. Continuous Holter ECG monitoring was used from the preoperative day to 48 hours postoperatively. The results showed that when myocardial perfusion was restored after the ischemic period during the coronary artery grafting, there was a significant difference in the incidence of VF, which developed in 79.1% of the control group but in only 48.8% of the patients in the preconditioning group. Postoperative nonsustained ventricular tachycardia (VT) developed in the majority of patients in the control group (97.7%) but in only 55.8% of the preconditioning group. As pointed out by the authors, although nonsustained VT during postcardioplegic reperfusion tends to be a benign, short-lived event, it is usually considered to reflect ischemia/reperfusion injury. Postoperative sustained VT occurred in 3 control patients but in none of the patients in the preconditioning group. Therefore, in these patients, there seems little doubt that the incorporation of the preconditioning protocol reduced the incidence of these arrhythmias. This is important because VT and VF are two of the main potentially life threatening complications after coronary artery bypass surgery, and the present work suggests a possible therapeutic strategy. The possibility of a practical application is enhanced by the relatively brief period of preconditioning ischemia used. In this study, the preconditioning protocol used two 2-minute periods of ischemia. Although this might be considered rather short to induce preconditioning, it seems to have been sufficient to achieve an effect in these patients undergoing surgery. Also of importance is the fact that this study provides for the first time...
evidence of an antiarrhythmic effect of preconditioning in humans.

The reason why studies on preconditioning have consistently shown a reduction in infarct size even though the effect on arrhythmias has been both antiarrhythmic and proarrhythmic is not clear. The mechanisms that either trigger or mediate preconditioning are complex. One of the major effectors of preconditioning is thought to be the K$_{\text{ATP}}$ channel. Traditionally, it was thought to be the sarcolemmal K$_{\text{ATP}}$ channel that was involved. Activation of the sarcolemmal K$_{\text{ATP}}$ channel during ischemia shortens the action potential duration (APD). It was therefore proposed that activation of the K$_{\text{ATP}}$ channel during the preconditioning ischemia would result in APD shortening and hence less time available for calcium entry into the cell during the action potential plateau. This reduced Ca$^{2+}$ influx would slow the loss of ATP, thereby lessening the ischemic insult and infarct size. Because the refractory period roughly corresponds to APD under normal conditions, shortening of APD by K$_{\text{ATP}}$ activation would lessen the ischemic insult and infarct size. Because the refractory period roughly corresponds to APD under normal circumstances, shortening of APD by K$_{\text{ATP}}$ activation would be expected to result in shortening of refractoriness that in turn could be proarrhythmic. Such a concept, however, is not straightforward, because during ischemia, the voltage dependence of refractoriness is lost and the refractory period may outlast the action potential by several hundred milliseconds. Refractoriness is therefore no longer determined by APD then. This phenomenon, known as post-repolarization refractoriness, occurs within the first few minutes of ischemia in animals and in humans as early as the first minute of ischemia. This would be expected to nullify the proarrhythmic effect of APD shortening as a result of the K$_{\text{ATP}}$ channel activation. Post-repolarization refractoriness is largely the consequence of local extracellular potassium accumulation. In the border zone between the nonischemic and ischemic area, potassium diffuses from the ischemic to the normal territory. Therefore, in the border region, where extracellular potassium may approximate to normal values, refractoriness may correspond to APD and accelerated shortening of APD during ischemia will be accompanied by a corresponding shortening of refractoriness, which would be proarrhythmic. It is worthy of note that it is the border zone from which the majority of ischemic arrhythmias arise. The reason for the inconsistent effects of preconditioning on arrhythmias, ie, antiarrhythmic or proarrhythmic, has not been established. We may speculate on possible explanations, however. It seems likely that species differences play a role, with predominantly antiarrhythmic effects observed in canines and rodents and proarrhythmic effects seen in pigs and rabbits. The time course of post-repolarization refractoriness seems to vary markedly between species. It is therefore likely that substantial differences exist between different models and species in the regional distribution of refractoriness and excitability as outlined above, which could have a marked effect on the susceptibility to arrhythmia. More recently, the participation of the sarcolemmal K$_{\text{ATP}}$ channel in preconditioning has been questioned on the basis of several observations, including the fact that a preconditioning effect does not seem to depend on APD shortening or even on the presence of action potentials at all. The mitochondrial K$_{\text{ATP}}$ channel seems to be important in preservation of the myocardium by preconditioning. It is possible that future work may show a key role for the mitochondrial K$_{\text{ATP}}$ channel as either proarrhythmic or antiarrhythmic. At the present time, the role of both the sarcolemmal and mitochondrial K$_{\text{ATP}}$ channel in arrhythmogenesis is uncertain. Several other mediators and triggers of preconditioning have been established that may play a role in the initiation and/or maintenance of ischemic arrhythmias. A recent study in dogs suggests that preconditioning may exert an antiarrhythmic effect during ischemia by modifying cardiac autonomic receptor mechanisms, which results in an enhanced parasympathetic/sympathetic balance. These authors propose that this may be the consequence of the release of endogenous substances, particularly nitric oxide acting to inhibit noradrenaline in the ischemic myocardium. Sympathetic activation may be arrhythmogenic by several mechanisms, including shortening of refractoriness, enhancing automaticity and thereby encouraging firing of automatic foci, and the development of both early and late afterdepolarizations, thereby encouraging triggered activity. Several different electrophysiological mechanisms may be involved in the initiation and maintenance of arrhythmias in the setting of ischemia, including each of the above. Exactly how preconditioning prevents, modifies, or initiates these arrhythmias remains to be determined. Perhaps in time the sarcolemmal K$_{\text{ATP}}$ channel may be granted a reprieve and assigned a role of arrhythmogenesis alongside but independent from the more mainstream mechanisms determining tissue necrosis orchestrated by the mitochondria.

In the meantime, Wu and colleagues should be congratulated on their study and for providing convincing evidence that preconditioning may protect against ischemia/reperfusion arrhythmias in humans. This should further fuel endeavors to find answers to the multiplicity of questions surrounding the effect of preconditioning on arrhythmogenesis. Up to now, the basic science investigation of the effects of preconditioning on arrhythmias in animals has been insignificant compared with the extensive research examining limitation of infarct size and tissue necrosis. Perhaps the study by Wu and colleagues will help redress the balance.

References


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