EDITORIAL COMMENT

Myocardial Response to Ischemic Preconditioning: Is it a Novel Predictor of Prognosis?*

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Ischemic preconditioning (IP) was originally defined as the enhancement of myocardial tolerance against infarction induced by a brief sublethal episode of ischemia in experimental animals (1,2). Subsequently, the concept of IP was expanded and currently includes protection against myocardial stunning, arrhythmia, and vascular dysfunction after ischemia/reperfusion injury (3–6). Results of clinical studies conducted over the past decade support the notion that IP occurs in human hearts, with one such situation being pre-infarct angina, which has been shown to protect patients with myocardial infarction in terms of infarct size, contractile dysfunction, vascular response to thrombolytic agents, and prognosis (7–11).

Although no quantitative measurement was made for coronary collaterals in this study, collateral recruitment is unlikely to be a major mechanism of IP detected at the second 90-s coronary occlusion. Firstly, ST elevation during the first balloon inflation was significantly larger in the IP responders than in the non-IP responders, and this finding argues against the possibility that the IP group included more patients with developed coronary collaterals. Secondly, the duration of coronary occlusion was short (90 s), and the number of coronary occlusions was small for recruitment of collateral flow. An earlier study by Billinger et al. (15) showed that collateral flow significantly increased at the third but not at the second 120-s coronary balloon inflation. Even then, such an increase in collateral flow could account for only 30% of the change in ST shift, indicating the presence of a collateral flow-independent mechanism. Thirdly, attenuation of ischemia-induced ST elevation by IP has been demonstrated in swine hearts, which essentially lack coronary collaterals (16). Taken together, these findings suggest that patients who failed to show ECG phenotype of IP had lost their myocardial ability to respond to IP stimuli.

Because ST shift is a surrogate end point of IP, the preserved response to IP identified by this end point does not necessarily ensure that IP mechanisms against infarction, arrhythmias, and vascular injury are indeed preserved. However, there are overlaps in the mechanisms of IP against each of these end points (2–6), which generally consist of signal transduction triggered by activated G-protein-coupled receptors (GPCRs), leading to activation of end-effectors, including the ATP-sensitive K⁺ channel (KATP channel). Theoretically, impairment of any of these steps should make the heart non-responsive to IP stimuli. In fact, we recently found that post-infarct ventricular remodeling impairs the IP mechanism by interruption of its signal transduction (17,18). Clinical studies using ST shift as an end point of IP have suggested that α-adrenergic, adenosine, and opioid receptors as well as KATP channels contribute to IP in human hearts as in experimental animals (19). Furthermore, a crucial role of the KATP channel in IP protection as a mechanism downstream of the GPCRs has been demonstrated in human cardiac tissues in vitro (20,21).

Therefore, a plausible explanation for the higher prevalence of diabetic patients in the non-IP responders is that autonomic diabetic neuropathy prevented IP ischemia from activating GCRP receptors relevant to IP. It is also possible that sulfonylureas administered for plasma glucose control blocked cardiac KATP channels, preventing IP response in some diabetic patients. Association of female gender with lack of response to IP is an interesting finding and warrants further investigation because a recent study has shown that IP failed to reduce infarct size in oophorectomized female mice (22).

The significant association between loss of myocardial response to IP and poor prognosis is an important novel finding in the study by Laskey and Beach (14). This

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association could be either causally related or a result of association via a common cause. However, clinical evidence supports the notion that angina protects human hearts from lethal and sublethal cardiac events. In addition to protective effects of pre-infarct angina on prognosis after infarction, there are two other notable features of angina or a brief ischemic episode that would prevent cardiac events. One is the improvement of coronary endothelial function, and the other is suppression of ischemia-induced arrhythmias. Endothelial dysfunction is of prime importance in development of atherosclerosis and cardiovascular events (23–25), and IP protects coronary endothelial function in animal models of ischemia/reperfusion injury via opening of the $K_{ATP}$ channel (5,6). Furthermore, such vascular protective effects of IP have been demonstrated in humans (26), and the Impact of Nicorandil in Angina (IONA) trial (27) showed that a $K_{ATP}$ channel opener significantly reduced the incidence of cardiac events in high-risk stable angina patients. Anti-arrhythmic effects of IP in humans (28,29) may be even more important because ventricular arrhythmias are believed to be a major cause of pre-hospital death in patients with acute myocardial infarction. A recent study by Edwards et al. (28) demonstrated that IP with exercise-induced myocardial ischemia not only suppressed ST shifts but also markedly reduced ventricular arrhythmias, including ventricular tachycardia and fibrillation, during subsequent ischemia. Taken together, circumstantial evidence favors a causal relationship between myocardial response to IP at the time of PCI and improved prognosis after PCI.

Regardless of the reason, the close association of ECG phenotype of IP at the time of PCI with prognosis in patients with coronary artery disease indicates that ST-shift response during PCI may be useful for stratifying the risk of future cardiac events. However, several questions need to be answered to characterize the ST response to IP as a risk factor. Is the criterion of IP in the present study (i.e., more than 33% reduction of ST elevation during coronary balloon inflation) the most appropriate for identifying patients at high risk? Is there no difference between causes of death in the IP responders and non-responders? Do any of the pharmacologic agents interfere with the validity of the ST shift for detecting IP? This issue is particularly important for diabetic patients receiving sulfonylurea, because this agent inhibits the sarcolemmal $K_{ATP}$ channel that contributes to ischemia-induced ST shifts (30). Another drug that can modify ischemia-induced ST shift is nitroglycerin, which could mimic IP (31). Large-scale clinical studies are necessary to address these questions in the future.

**REFERENCES**


