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EDITORIAL COMMENT

Percutaneous Transluminal Coronary Angioplasty as a Model of Ischemic Preconditioning and Preconditioning-mimetic Drugs*

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The concept of ischemic preconditioning refers to myocardial protection from ischemia-reperfusion insult by preceding brief ischemic episodes (1). An extensive effort has been made to understand the time frames and underlying mechanisms of ischemic preconditioning because of the potential applicability of this phenomenon in the clinical setting, especially because "preconditioning-mimetic" agents may enable the development of a chronic state of tolerance to ischemia.

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Several studies have shown that during percutaneous transluminal balloon angioplasty (PTCA) there is amelioration of the severity of the ischemic response during repeated ischemia (2–15). In the PTCA model, the number, duration and severity of the brief ischemic episodes and the duration of the intervening reperfusion period can be controlled and monitored in addition to determining the recruitment of collateral circulation. Therefore, it is generally believed that this model resembles experimental animal models more closely than the acute myocardial infarction, warm-up angina and the cardiopulmonary bypass clinical models. The PTCA model has gained popularity as a tool for investigating the time frames and mechanisms of ischemic preconditioning in humans and has been used in studies assessing the ability of various agents to mimic or prevent preconditioning (5,15–21). In an article published in this issue of the *Journal of the American College of Cardiology,* Billinger et al. (22) used the same PTCA model to evaluate whether adaptation to repeated brief ischemic episodes and the protection afforded by intracoronary infusion of adenosine is mediated by recruitment of collateral flow or truly represents ischemic preconditioning. This study adds important information to our knowledge base regarding what happens during repetitive coronary artery occlusions in humans.

Several aspects of the PTCA model of ischemic preconditioning should be discussed, because they have relevance to understanding and interpretation of this study.

The duration of the preconditioning stimulus. There is a threshold for induction of protection by ischemia, including the minimum time of each ischemic episode, the number of episodes and the total ischemic time required to confer protection that seems to be species dependent (23). Moreover, when the initial brief ischemic episode is too long, the protective effect might be lost (24). In humans, repeated balloon inflation of ≤1-min duration did not attenuate the ischemic response (17,25–29). Most of the investigators, but not all (30,31), found that 90 to 120 s of ischemia is effective in decreasing pain and ST deviation during the subsequent ischemia (2–6,10,15,19–21,32,33). In contrast to patients without recruitable collaterals, in patients with good collateral circulation, even two 150-s episodes of balloon inflation did not induce preconditioning (8). Thus, not only the duration, but the severity of ischemia, which is inversely correlated with the magnitude of collateral recruitment, is important in determining the protection afforded by the preceding ischemic episode. Billinger et al. (22) used 2 min of occlusion, which seemed to be appropriate.

Controlling for collateral recruitment. Recruitment of collaterals is another powerful protective mechanism against ischemia, independent of the metabolic "preconditioning mechanisms." In some patients, especially those with severe preexisting coronary narrowings, collaterals can be recruited during ischemia induced by balloon inflation and attenuate the ischemic response (8,29,34). Therefore, it is important to control for collateral flow, although not all studies control for collateral circulation. In some studies, baseline collateral circulation was assessed by coronary angiography (2,5,11,15, 20,27,28,30). However, coronary angiography only detects collateral vessels with a diameter >100 μm (35) and therefore, is not adequate for assessing the smaller collateral vessels that supply the myocardium. Some of the investigators assessed coronary collaterals by myocardial contrast echocardiography (8), flow velocity in the contralateral artery by Doppler-tipped intra-coronary guide wire (21), cardiac vein flow during balloon occlusion (2), or intracoronary wedge pressure measured distal to the balloon catheter (3,22). Billinger et al. used the intracoronary pressure-derived collateral flow index, accounting for the simultaneous measurement of mean aortic pressure and the estimate of the central venous pressure (22). One potential limitation of the present study is that the central venous pressure was estimated and was not directly measured. An

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optimal approach would be to document that during balloon inflation the central venous pressure remains constant.

There is debate in the literature as to whether collaterals can be further recruited on repeated balloon inflations. Cribier et al. (3) described that the number of patients who experienced pain during inflation and the intensity of pain progressively declined with subsequent balloon inflations. Collateral angiographic grade did not change in seven patients and increased in 10. Coronary occlusion pressure/mean aortic blood pressure increased in 8 patients and the average coronary occlusion pressure for all 17 patients was significantly higher during the fourth than the first coronary occlusion, indicating that in some patients further recruitment of collaterals can contribute to the adaptation to repeated ischemia. Even in those patients that did not recruit collaterals there were less angina and ST changes, suggesting that at least in those patients preconditioning may have been playing a role. However, others have found that no further collateral recruitment occurs during repeated balloon inflations (8,21). In contrast with these studies, Billinger et al. showed that 28 out of 30 patients had an increase in collateral flow between the first and third balloon occlusion, indicating further collateral recruitment (22).

The surrogate end points. Of course, the end point in this PTCA model of ischemic preconditioning or pharmacologic interventions cannot be infarct size, as in the classical model of ischemic preconditioning (1). Various surrogate endpoints have been used, mainly subjective estimation of the severity of pain (3–6,8,14–16,20–22,32,33), and quantification of the electrocardiographic changes (8,15,16,18,19,22,30).

Most studies have shown that the severity of pain diminishes during repeated balloon inflations. Pharmacologic interventions with preconditioning-blocking agents such as glibenclamide (5), aminophylline (19), or bamiphylline (20) prevents this adaptation. Leesar et al. reported that adenosine, a preconditioning–mimicking agent, alleviates pain compared with controls during the first ischemic period (15). In contrast, Billinger et al. (22) found no difference in chest pain score between the adenosine and placebo pretreated patients. It should be remembered that the severity of pain developed is dependent on several factors in addition to the preconditioning effect, including the duration of ischemia, recruitment of collaterals, psychological factors (the subjective perception of pain may be higher during the first unfamiliar episode) and the degree of stretching of the coronary artery wall by the balloon (4). Thus, estimates of the severity of pain can only be made in studies in which the duration of balloon inflations and the pressure used are kept constant (4) and the collateral flow in each ischemic episode is measured. Billinger et al. assessed collateral recruitment during each balloon inflation and used 2 min of coronary occlusion, however, it is not clear whether the same balloon inflation pressures were used (22). Therefore, some degree of caution may be needed in interpreting these data.

The magnitude of ST shift during ischemia has been used to monitor the "severity of ischemia" and the effects of various agents on amelioration or exacerbation of ischemia, and has been shown to decrease during repeated coronary occlusions (36). The magnitude of ST shift is highly dependent on the magnitude of collateral recruitment (8,29,36). On the other hand, reduction in the magnitude of ST shift with repeated myocardial ischemia without recruitment of collaterals has been shown in animal models (37). However, changes in the magnitude of ST shift are not a sine qua non for infarct size limitation, the classical endpoint of ischemic preconditioning, and caution should be paid in using the ST shift especially when the effects of pharmacologic agents are evaluated, because these agents may affect the ST-T segments without an effect on myocardial infarct size. For example, beta-adrenergic blocking agents attenuate ST shift during ischemia (27,28,36); however, most clinical studies have not shown a reduction of infarct size with beta-blockers (38).

Some investigators have used the surface electrocardiogram (8,11,15,30,32), others assessed the intracoronary electrocardiogram, obtained by connecting the guide wire to the V lead of the standard electrocardiogram (3–6,14–16,19–21,30), as was done in the present study (22). The intracoronary electrocardiogram is more sensitive than the surface electrocardiogram in detecting subtle changes in the ST amplitude during balloon inflation (15,39). It is unclear, however, whether ischemia induced by balloon inflation in different coronary artery segments may result in the same magnitude of ST shift. In the present study, Billinger et al. corrected the ST amplitude with the QRS amplitude (22). The uncorrected ST amplitude values are not presented. This method may correct the differences in the absolute magnitude of ST shift among patients undergoing angioplasty of different coronary artery segments. However, during PTCA there are changes in the QRS amplitude (40). It is unclear whether they corrected the ST amplitude with the baseline QRS or with the QRS in each evaluated complex. Whether correction used by Billinger et al. is superior to the common method of measuring the absolute ST amplitude remains to be validated.

ADENOSINE AND PRECONDITIONING IN RELATION TO THE PRESENT STUDY

There is extensive evidence supporting a prominent role for adenosine and its receptors in mediating the cardioprotective effects of ischemic preconditioning (41,42). Bamiphylline (20) and aminophylline (19), both adenosine receptor antagonists, abolished the attenuation of the ischemic response during repeated ischemia. On the other hand, intracoronary application of dipyridamole, an inhibitor of reuptake and degradation of adenosine, conferred myocardial protection during PTCA (18). However, in all these

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studies (18,19,20) collateral recruitment was not assessed; thus the effect of ischemic preconditioning was not separated from that of collateral recruitment. Kerensky et al. (16) reported that the mean intracoronary ST elevation during the first balloon inflation was comparable between the adenosine (intracoronary 100 μg) and placebo group, suggesting that adenosine pretreatment did not precondition the heart. The mean intracoronary ST elevation during the second balloon inflation compared with the first inflation was reduced in the placebo and increased in the adenosine group, suggesting that adenosine might have blocked the preconditioning effect (16). Leesar et al. (15) used a much higher dose of adenosine (intracoronary 20 mg infused over 10 min, starting 20 min before PTCA), and found that the adenosine group also had less intracoronary ST segment shift and less pain than the control group during each of these 2-min balloon inflations. However, although only patients with no angiographically visible collaterals at baseline were included in this study, collateral recruitment was not assessed (15). Therefore, it was unknown whether the protective effect is due to collateral recruitment, or due to metabolic "preconditioning-like" effect. The findings of Billinger et al. in the present issue contradict those of Leesar et al. (15). They randomized 30 patients to intracoronary saline or adenosine, using a greater adenosine dose than Leesar (24 mg over 10 min, starting 20 min before PTCA), and found that adenosine pretreatment was not associated with recruitment of collaterals or with attenuation of the ischemic response during the first balloon inflation (15). In contrast to Kerensky (16), but in accordance with Leesar (15), adenosine did not prevent further adaptation to repeated ischemia. Conversely, adenosine did not facilitate ischemic preconditioning, because intracoronary ST segment shift and chest pain scores during the second and third balloon inflations were similar between the control and the adenosine pretreated groups. Billinger et al. reported that the collateral flow index increased during repeated balloon inflations in both the control and adenosine groups (22). However, the correlation coefficient between the change in the ST segment shift and the change in collateral flow index was low, indicating that the progressive attenuation of the ischemic response could not be fully attributed to recruitment of collaterals and that additional factors, presumably ischemic preconditioning, are probably more important. However, it might be that the relationship between the ST shift and the collateral recruitment is not linear.

There are several important differences between Leesar's study (15) and the present study (22). Leesar et al. included only patients with no angiographically visible collaterals, whereas Billinger et al. also included patients with few collateral vessels on the first coronary angiography. Leesar et al. used 20 mg, and Billinger et al. 24 mg, of adenosine. It might be that at this somewhat higher dose the protective effect of adenosine is lost, as was seen after prolonged infusions (72 h) in the rabbit model (43). Leesar et al. permitted use of nitrates, whereas none of the patients in Billinger's study received nitrates. It is unknown whether there might be a synergistic effect between adenosine and nitrates. Billinger et al. assessed the intracoronary ST amplitude at 60 s of ischemia (22) and normalized it to the QRS amplitude, whereas Leesar et al. presented the absolute ST amplitudes, measured at 2 min of ischemia (15). One minute of ischemia may not be enough, because the ST shift is not fully evolved after 60 s. Cribier et al. showed that at 2 min of ischemia the differences in the magnitude of the intracoronary ST shift were more significant than those observed at 1 min of ischemia (3). In addition, Billinger et al. did not present how many of their patients had unstable angina. These patients might have been already fully preconditioned or in the refractory phase, as was mentioned in the first section.

In summary, Billinger et al. showed that recruitment of collaterals does occur during repeated balloon inflations. This is an important observation that should be considered in future PTCA-preconditioning protocols. However, the recruitment of collaterals could not fully explain the adaptation to repeated ischemia. Ischemic preconditioning is probably still an important mechanism for conferring adaptation to repeated ischemia, besides recruitment of collaterals in these patients.

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