Coronary angioplasty as a model of ischaemic preconditioning: fact or fancy?

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It is well established in the laboratory that brief periods of myocardial ischaemia can markedly reduce necrotic damage and arrhythmias during a subsequent period of ischaemia. This remarkable manifestation of adaptation to ischaemic stress, ischaemic preconditioning, has been investigated extensively in various animal species. The idea that preconditioning is mediated by endogenous protective substances has proved attractive to investigators, possibly because definable paracrine mediators could provide the chemical templates for the development of new therapeutic entities. So far, the vast research effort to unravel the cellular mechanisms of this powerful response has resulted in a picture of Daedalean complexity. In part, this complexity may be ascribed to major differences in the endpoints of ischaemic damage used to assess the preconditioning response in different laboratories. A further source of complication resides in species differences: even when the same endpoint is used (e.g. necrosis) there are marked differences in the apparent mechanism of preconditioning between one animal species and another. In view of these species differences, the need for elucidation of the mechanisms in man is pressing.

Examination of preconditioning has been extended to human myocardium in a variety of ways which ingeniously circumvent the obvious ethical issues associated with the experimental application of ischaemia to in situ human myocardium. For example, preconditioning of human myocardial tissue has been examined in vitro using isolated atrial trabeculae and human isolated cardiac myocytes. There have also been studies examining the potential for preconditioning human myocardium in situ during elective procedures in which ischaemia is induced routinely. These studies have been conducted during coronary artery by-pass grafting using the cross-clamp fibrillation technique in which the heart is subjected to repeated ischaemic arrest, and during percutaneous transluminal coronary angioplasty where repeated balloon inflation induces sequential brief periods of myocardial ischaemia. An example of this latter approach to investigating preconditioning is reported by Tomai and colleagues in the current issue. In this study, two sequential angioplasty balloon inflations were performed in patients undergoing elective angioplasty for stable angina. The authors determined three endpoints of ischaemia severity — intracoronary electrocardiographic ST segment elevation, surface electrocardiographic ST segment elevation and subjective pain score — and compared these during the first 2 min balloon inflation and the second balloon inflation. During the second inflation, ST shifts were attenuated, as was the pain score, suggesting that the severity of ischaemia was less during the second inflation. This apparently
The first description of preconditioning defined a phenomenon which delayed the onset of necrosis. Since then, the anti-arrhythmic effects of preconditioning have been reported as well as various surrogate endpoints of tissue tolerance, including indices of metabolic state, enzyme efflux, and myocardial contractility. Whether or not ST segment elevation during balloon inflation constitutes a realistic endpoint of ischaemia severity (or tissue tolerance) is a debatable point. In the absence of any clear definition from laboratory practice of what is universally acceptable as a 'hard' endpoint in preconditioning studies, apart from necrosis, it would be unwise to reject ST segment changes as an index of ischaemia severity. A recent study by Cohen et al. showed that attenuation of ST segment changes during repeated coronary occlusions in the rabbit, a species with negligible collateral flow, was abolished by adenosine A1 receptor blockade, as was the infarct-limiting effect of preconditioning. Thus it might be the case that the mechanism of ST shift attenuation by preconditioning in the rabbit is the same as the mechanism accounting for delay in cell death.

When the effects of coronary collateralization are excluded, coronary angioplasty presents a novel method for investigating ischaemic preconditioning in human myocardium. No method of investigation is without its limitations, and results obtained from angioplasty studies should be interpreted cautiously and not in isolation. Nevertheless, clinical investigation of preconditioning is still a relatively new pursuit, full of practical difficulties and unlikely to provide the rigorous endpoints of injury that laboratory studies can yield. Therefore, Tomai et al. are to be commended. Their study shows for the first time in situ that a form of preconditioning occurs during coronary angioplasty that is mediated by A1 receptor activation. At first sight this study suggests that a form of preconditioning occurs during coronary angioplasty that is mediated by A1 receptor activation. Certainly, this finding concurs with reports that the A1 receptor mediates preconditioning in the rabbit and the pig and also in isolated human atrial muscle and in human cardiomyocytes. Furthermore, this report extends the authors' previous work with the same angioplasty model in which it was shown that the adaptive response was abrogated in patients who were given glibenclamide, an inhibitor of ATP-sensitive K+ (KATP) channel activation. Again, that study paralleled laboratory research insofar as the involvement of KATP channels has been implicated in the preconditioning response in at least two animal species (pig and dog) and in isolated human atrium. However, what are we to make of balloon angioplasty as an in vivo model of preconditioning in man? Is this anti-ischaemic effect of the first balloon inflation attributable to preconditioning, or is it something else?

It is clear from laboratory studies that preconditioning is not dependent on the opening of preformed coronary collateral vessels. Measurements of collateral blood flow in dogs are consistently similar between control and preconditioned animals. In other species in which preconditioning has been demonstrated, notably the rat, rabbit and pig, there is no basal collateral flow. Man, of course, is different, and particularly with long-standing coronary artery disease there may be substantial collateral vessel development which may be recruited during acute ischaemic episodes. This fact imposes a major limitation on studies of preconditioning in clinical situations involving regional myocardial ischaemia such as coronary angioplasty. Some earlier studies assessing severity of myocardial ischaemia during sequential angioplasty balloon inflations have examined the contribution of collateral recruitment (see reference 7 for a review of these studies). For example, Heibig et al. reported a patient in whom ST deviation and chest pain were observed during the first balloon inflation but not during subsequent inflations, but this effect was probably related to the acute recruitment of collateral vessels. In a study by Deutsch et al., patients experienced less anginal pain, less lactate production and less ST segment deviation during the second balloon inflation and this modification of ischaemia did not appear to be due to an increase in collateral flow. In a subsequent study by Cribier et al., chest pain and ST segment changes were also attenuated during the second balloon inflation but there was opening of collateral vessels after the first inflation in 10 out of 17 patients. It would seem then that some patients during angioplasty may demonstrate a preconditioning-like response; in others the apparent benefit may be due to collateral recruitment, which is not preconditioning. Therefore, an obstacle to the interpretation of the study reported by Tomai et al. is that the contribution of the collateral blood supply has not been excluded as a possible — and plausible — explanation for their observations.
An unresolved, persisting challenge for percutaneous transluminal coronary angioplasty: how to identify the lesions that will not restenose

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In this issue, Hamon et al. [1] describe the vasomotor response of coronary segments to ergonovine about 6 months after successful percutaneous transluminal coronary balloon angioplasty. The study demonstrates a small, but significantly greater, degree of constriction to a low dose (100 μg) of ergonovine at the site of angioplasty compared to that observed at proximal and distal sites, independent of the occurrence of restenosis at 6 months post-percutaneous transluminal coronary balloon angioplasty. In spite of the failure of ergonovine to cause occlusive or subocclusive epicardial coronary artery ischaemic signs in any of the patients included in the study, anginal pain with >1 mm ST-segment depression developed in five patients in response to the low dose. The constrictor response was similar at the dilated site and in proximal and distal segments at a high dose (300 μg), indicating a displacement to the left of the dose–response curve at the lower dose of this agonist in dilated segments irrespective of the occurrence of restenosis.

Three major lessons can be learned from the study:

First, in a carefully selected group of patients, which excluded those with unstable or variant angina (and probably also some with very early clinical evidence of restenosis), the mechanical trauma of balloon angioplasty appears insufficient to cause local vascular hyper-reactivity to ergonovine, such as that observed in variant angina [2]. The study was not designed to establish whether the mild displacement of the dose–response curve observed at the dilated site is caused by endothelial dysfunction or by enhancement of the local constrictor response of the smooth muscle due to the local proliferative response and/or to the increase in muscle cell mass. Irrespective of its cause, the degree of enhanced constrictor response at the dilated site documented in this study is not only insufficient to impair resting flow, but is also unlikely to limit the increase of flow through non-critically restenosed arteries during moderate or submaximal exertion.

Second, the development of angina with ST-segment depression in the absence of occlusive or subocclusive spasm, observed in some patients, indicates an enhanced vasoconstrictor response of distal coronary vessels capable of reducing critically restenosed coronary flow. Thus, during their daily lives, such patients could develop episodes of myocardial ischaemia because of distal coronary vessel constriction. This alternative mechanism of ischaemia cannot easily be substantiated in the presence of either a stenosis or a restenosis, but it has already been postulated to explain the variability in ischaemic threshold in a rather special group of patients with chronic stable angina [3]. The reasons why some