Neglect of the coronary circulation: some critical remarks on problems in the translation of cardioprotection

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Acute myocardial infarction remains a significant health problem throughout the world, and for those patients surviving the immediate event, infarct size is the main determinant of further prognosis.1–3 Timely reperfusion, as originally reported in dogs by John Ross Jr over 30 years ago,4–6 is still the only way to reduce ultimate infarct size but comes also at a price and induces injury in itself.7,8 Ischaemic preconditioning and ischaemic postconditioning, again originally both reported in dogs,9,10 reduce infarct size—provided there is also reperfusion!11–15 Although the phenomena of ischaemic pre- and postconditioning have stimulated research on the pathobiology of myocardial ischaemia and reperfusion in general, and notably on endogenous protective signalling mechanisms,12,16 their value has thus far remained mostly paradigmatic. The translation of experimental findings to patients with acute myocardial infarction has remained somewhat inferential for ischaemic preconditioning11 and has been limited to small-scale proof-of-concept studies in highly selected patients17,18 or retrospective analyses19 for ischaemic postconditioning, but has not yet been successful as a therapeutic reality. Obvious problems in the translation of cardioprotection from the experiment to the clinic have been critically reviewed before,13–15,20 including the choice of species and model to mimic the human situation, the choice of the potentially cardioprotective molecule/drug, the design of the clinical trial with respect to dose and time of treatment, and the selection of patients with respect to size, site and collateralization of their infarcting myocardium, their age,21 co-morbidities, and co-treatments.22

Surprisingly, the coronary circulation, which is the ultimate culprit of acute myocardial infarction, has been neglected as a potential problem in the translation of experimental findings from animals with sudden occlusion and immediate reperfusion of otherwise healthy normal coronary arteries to humans with pre-existing coronary artery disease of varying extent and duration. Here, we focus on three aspects: (i) coronary microembolization prior to acute myocardial infarction, (ii) incomplete reperfusion following acute myocardial infarction, and (iii) interference of cardioprotective signalling with coronary artery disease and its treatment.

1. Coronary microembolization prior to acute myocardial infarction

The rupture of an atherosclerotic plaque in an epicardial coronary artery does not always result in subsequent thrombotic occlusion and impending myocardial infarction; milder forms of plaque rupture may leave some residual blood flow and result in the embolization of atherothrombotic debris into the coronary microcirculation.23,24 In fact, overt myocardial infarction is probably the tip of the iceberg, and transient episodes of angina often precede myocardial infarction. Such short ischaemic episodes may either protect the myocardium by ischaemic preconditioning11 or damage it when associated with coronary microembolization. Common to both ischaemic preconditioning and coronary microembolization is the involvement of adenosine. However, in anaesthetized pigs, prior coronary microembolization with microspheres of 42 μm diameter failed to protect the myocardium from infarction after sustained ischaemia and reperfusion.25 The superimposition of infarction induced by coronary microembolization per se even increased the final infarct size after sustained ischaemia in microembolized myocardium.26 Also, a potential loss of protection by ischaemic preconditioning secondary to a critical loss of adenosine through enhanced washout was not observed. Following coronary microembolization, a preconditioning stimulus still induced the mandatory transient increase in the interstitial adenosine concentration and reduced infarct size.27

Whereas coronary microembolization neither induces nor interferes with acute ischaemic preconditioning, protection is observed several hours following coronary microembolization when myocardial TNFα expression is increased and, vice versa, protection is abolished by TNFα-neutralizing antibodies.28 Therefore, coronary microembolization can elicit a 'third window' of preconditioning between the classical 'first window' and the delayed 'second window' of...
preconditioning that is triggered by inflammation, and it may be difficult to detect any protection by classical ischaemic pre- or postconditioning on top of this.

Although ischaemic pre- and postconditioning reduce the infarct size resulting from epicardial coronary artery occlusion and reperfusion, it is entirely unclear whether or not they can also protect from the microinfarction resulting from coronary microembolization—possibly not, because there is no reperfusion! This problem relates particularly to studies attempting to provide proof-of-concept for cardioprotective strategies in cardiac surgery. Ischaemic global cardiac arrest under cardiopulmonary bypass with protection by hypothermia, cardioplegia, or intermittent cross-clamping is used to prevent myocardial infarction, and the post-operative release of creatine kinase or troponin probably reflects microinfarction secondary to surgical trauma, iatrogenic coronary microembolization, and/or heterogeneously incomplete protection; again, it is difficult to detect true protection by ischaemic pre- or postconditioning and also by remote preconditioning in this setting, and the available data that suggest protection must be interpreted with great caution.

2. Incomplete reperfusion following acute myocardial infarction

Reperfusion is mandatory for the salvage of infarcting myocardium, but it induces irreversible damage itself. Consequently, modification of reperfusion is an option to both salvage infarcting myocardium and to attenuate reperfusion injury. Long before the first description of ischaemic postconditioning, gentle reperfusion was known to attenuate damage after ischaemia. However, whether or not infarct size was reduced by gentle reperfusion remained controversial. In the more artificial model of isolated, saline-perfused rat hearts, reperfusion at reduced perfusion pressure reduces infarct size, and this protection involves inhibition of mitochondrial permeability transition pore opening. Infarct size is also reduced by gentle reperfusion in dogs with staged reperfusion at a perfusion pressure of ~50 mmHg for 20 min. Likewise, infarct size is reduced in dogs by gentle reperfusion when a coronary occluder is slowly released over 30 min, although this could not be confirmed in another study using a similar protocol. We have recently demonstrated in anaesthetized pigs subjected to 90 min low-flow ischaemia that slow restoration of blood flow back to baseline during 30 min of reperfusion reduces infarct size by ~20% when compared with immediate full reperfusion.

In humans undergoing primary percutaneous interventions for acute myocardial infarction, full TIMI 3 flow is not achieved in 5–15% of patients, and the angiogram is usually taken several minutes into reperfusion when both reperfusion injury and protection from it might have already occurred. In humans undergoing thrombolysis for acute myocardial infarction, the time course of reperfusion is not known, but it is probably always slow and gentle. When reperfusion is not immediate and complete but gentle, some protection will also occur in the control group, and it will be more difficult to obtain evidence for protection by either ischaemic pre- or postconditioning in any clinical trial. Even apparent full and immediate reperfusion on angiography may be misleading since coronary blood flow during reperfusion may be very heterogeneous and reflect areas with reactive hyperaemia and others with persistent ischaemia. Coronary microembolization of atherothrombotic debris with interventional re-opening of a thrombotic epicardial coronary artery occlusion with underlying plaque rupture may both cause microcirculatory ischaemia with subsequent microinfarction and induce hyperaemia in surrounding myocardium. Finally and obviously, collateral blood flow during ischaemia and reperfusion cannot really be determined using coronary angiography, and PET flow data from patients during acute myocardial infarction and/or during immediate reperfusion are not available.

3. Interference of cardioprotective signalling with coronary artery disease and its treatment

The cellular and/or subcellular origin of most cardioprotective signalling molecules is not firmly known, and it is probably too simplistic to attribute the entire cardioprotective program to cardiomyocytes. In fact, the vascular wall, with its endothelium, smooth muscle cells, perivascular nerves, and—notably with atherosclerosis—inflammatory cells, may be a significant source of pertinent signalling molecules: e.g. adenosine, bradykinin and nitric oxide originate from the endothelium, TNFs originate not only from cardiomyocytes but also from mast cells and macrophages and norepinephrine, opioids, and other peptides may originate from perivascular nerves. The formation and release of all of these signalling molecules is probably altered with coronary artery disease and its treatment; in fact, endothelial dysfunction and inflammation are essential alterations in atherosclerotic coronary vasculature. It appears that with coronary atherosclerosis, protection by ischaemic preconditioning is better preserved than that by ischaemic postconditioning.

Most treatment options for coronary artery disease also interfere with the haemodynamic determinants of infarct size and/or the signalling of ischaemic pre- and postconditioning. β-blockers and selective bradycardic agents reduce infarct size. β-Adrenergic signalling is involved in protection by pre- and postconditioning, and accordingly β-blockade can abolish such protection. On the other hand, ischaemic postconditioning is lost in rat hearts with chronic coronary stenoses and protection is restored by carvedilol. The protection by the selective bradycardic agent ivabradine is still achieved when given in a postconditioning mode just before reperfusion and is not dependent on heart rate reduction but may involve a free radical mechanism. ACE inhibitors, AT1 blockers, and their combination reduce infarct size and involve signalling of bradykinin and cyclooxygenase, which are also essential elements of pre- and postconditioning. It is not really clear whether or not nitroglycerin and NO-releasing drugs induce cardioprotection through the signalling mechanisms of ischaemic pre- and postconditioning, and activation of protein kinase G by enhanced levels of cGMP is clearly cardioprotective. Statins induce cardioprotection using in part the same signalling mechanisms as ischaemic pre- and postconditioning, but their chronic use also interferes
with these signalling mechanisms and can actually eliminate protection. In conclusion, the coronary circulation is a major determinant of the success of ischaemic pre- and postconditioning, and neglect of the coronary circulation is to a significant extent responsible for the problems in translation of cardioprotection to the clinic.

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