Stunning: Three questions and concerns

Introduction

Of all the manifestations of left ventricular dysfunction, myocardial stunning must be the most exhaustively investigated. More drugs have been evaluated in the canine model of stunning than in any other model but, despite this, several fundamental questions about this phenomenon remain unanswered. In the following, I pose three questions and anticipate some of the answers.

Is stunning really the definitive example of "reperfusion injury"?

I, as others, have written on the phenomenon termed "reperfusion injury", discussing its nature and even its existence (3). Reperfusion injury can be simply defined as deleterious events, occurring during reperfusion (and arising as a consequence of reperfusion) that subtract from the benefits of the restoration of flow and thereby increase tissue injury over and above that sustained during the preceding period of ischaemia. Stunning is frequently cited as a classic example of such injury, and evidence for the existence of a deleterious component of reperfusion usually derives from the observation that interventions given only during reperfusion are able to attenuate stunning. Thus Bolli et al. (1) have shown that a free radical scavenger given only (and transiently) at the time of reperfusion can dramatically attenuate stunning in the canine heart. However, can this really be taken as definitive evidence of the existence of reperfusion injury? Whilst the administration of a drug after a period of ischaemia cannot lessen the amount or nature of the injury sustained during that period, I remain sceptical that such experiments provide definitive proof for the existence of reperfusion injury. If my following arguments are correct, it becomes important so question whether stunning is necessarily an example of reperfusion injury (a situation that would in no way diminish the significance of stunning).

It seems to me that a finite amount of time is always required for tissue to recover from a transient pathological insult. Why then should a piece of myocardium that has sustained reversible (but nonetheless metabolically and functionally devastating) ischaemic injury be expected to recover fully and immediately on the restoration of flow? Why should the myocyte be denied a reasonable period to re-instate its metabolic and ionic homeostasis before returning to full contractile activity? Can we not view the stunned myocardium as a well-regulated tissue undergoing a controlled period of convalescence? Why can we not assume that the salutory effects of interventions given at the time of reperfusion are merely accelerating the recovery of some (as yet unknown) metabolic process sustained during ischemia in a manner akin to an aspirin hastening the departure of an alcoholic hangover? Would anyone argue that part of the hangover is a consequence of stopping drinking? Why should we not consider stunning as an "ischaemic hangover"?

It follows from the above argument that it is impossible to prove the existence of a deleterious component of...
reperfusion simply by adding an intervention at the time of reperfusion and looking for benefit. We may, however, stand a better chance if we endeavour to attenuate stunning (or any other putative manifestation of reperfusion injury) by removing a component of the reperfusion process and demonstrating clear benefit. Such experiments are more difficult to devise, but some do exist, such as transient leucocyte depletion at the time of reperfusion—and what a controversial field this has become!

Even if reperfusion injury does exist, and assuming that it makes a contribution to stunning, we should ask: what fraction of the contractile deficit should be attributed to reperfusion injury and what fraction reflects convalescence from the injury sustained during the period of ischaemia? With rare exceptions (2) this question is hardly ever discussed—despite the likelihood that the answer could be of major importance to understanding the mechanisms of stunning. The fact that interventions given (sometimes in combination) at the time of reperfusion, have never been shown to totally abolish the phenomenon, must add to the common-sense view that a substantial proportion of the contractile deficit must be attributable to convalescence from ischaemic injury. The recent studies showing that the pre-ischaemic administration alone of interventions such as ATP-sensitive potassium channel openers can result in a substantial attenuation of post-ischaemic stunning, can only add weight to this argument. In the absence of any data, should we perhaps agree that as much as half of the contractile deficit of stunning may be unrelated to reperfusion injury?

Has something been omitted from the description of stunning?

Figure 1A is representative of many hundreds of figures in the literature, and is fully consistent with the accepted definition of stunning as a post-ischaemic contractile deficit that takes hours or days to normalise. Almost without exception investigators portray the recovery profile as one the progressively improves from a very low value at the onset of reperfusion. However, this does not adequately portray the dynamic nature of the contractile recovery during the early moments of reperfusion, when a potentially important, but generally ignored, event occurs. Most investigators, know that the profile for functional recovery is in fact biphasic (Figure 1B) with an early, and often complete, recovery of contractile function. This recovery is, however, transient, and after a few minutes contractile function declines again (sometimes to zero) to be followed by a very slow recovery. Possibly, most investigators do not record function until 15 min or so into the reperfusion period. Nonetheless, failure to record or discuss this early recovery must be to the detriment of our understanding of myocardial stunning.

It could be argued that the early and rapid recovery might be a consequence of some transient inotropic stimulus such as reperfusion-induced release of catecholamines or intracellular calcium overload; certainly the stunned heart possesses considerable inotropic reserve. However, an alternative interpretation is that the heart has the potential to recover rapidly and fully from the ischaemia-induced injury, but this is halted and reversed by the onset of reperfusion injury, which accounts for the secondary decline in function. Is it a coincidence that the curtailment of the early recovery of function appears to coincide temporally with the burst of free radical production that has often been suggested as responsible for the induction of

Fig. 1 A Traditional representation of the recovery profile for myocardial stunning. B The more complete representation of the profile showing the early, transient, hyperdynamic phase that is rarely reported or discussed in the literature.