Cardioprotection: The Disconnect Between Bench and bedside

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Early reperfusion by primary percutaneous intervention in patients with ST-segment elevation myocardial infarction (STEMI) limits infarct size and preserves left ventricular systolic function, thereby improving prognosis. Despite this process of restoring blood flow to salvage the myocardium, further myocardial damage can occur as a consequence of reperfusion; this is known as myocardial "ischemia-reperfusion" injury (IRI).

Many cardioprotective therapies aimed at reducing IRI have been successfully examined in the preclinical setting. Despite attenuating IRI at the bench, not all have subsequently demonstrated a reduction in infarct size at the bedside, and none have demonstrated clinical benefits.

The failure to translate cardioprotective therapies into the clinical setting can be attributed to many factors, from inadequate animal models of infarction to poor clinical study designs. Overall, it seems that hopes are fading that any cardioprotective intervention will ever materialise. However, after thoroughly dissecting the issues, we have come to a relevant diagnosis, which we term as a "disconnection paradigm". This condition refers to the complete disconnect between preclinical and clinical studies in cardioprotection.

STEMI is linked to multiple cardiovascular risk factors and co-morbidities, and it is also intensively treated both acutely and chronically. These concomitant co-morbidities and medications induce alterations in myocardial cellular signalling cascades, thereby affecting both the sensitivity to IRI and the response to any cardioprotective intervention. Many examples can illustrate the problem with co-morbidities[1]. Diabetes mellitus makes the heart more susceptible to IRI and make less effective conditioning therapies, and aging changes both the pharmacokinetics and pharmacodynamics of cardiovascular drugs as well as affects the susceptibility to be protected. There has only been a mild response to address this issue, using old and diabetic animals[2].Less attention has been paid to concomitant medications, despite most STEMI patients receiving acute treatment with aspirin, P2Y12 inhibitors, statins, opioids, beta blockers and anticoagulation agents, (according to the management guidelines[3]) with many of the above being shown to have a cardioprotective effect.

Despite this complex clinical picture, it is surprising how all these factors are systematically ignored in the preclinical setting where concomitant medications are never assessed. This disconnection between preclinical study designs and clinical reality may justify our failure to translate cardioprotective therapies into clinical practice.

As a treatment for this disconnect disorder, we propose to make a counter intuitive step: cardioprotection needs to go backward before it can be moved forward. There is a need to fill this translational

gap between bench reductionist models and this increasing complex reality. We suggest adding an extra step in our current translational approach to approximate bench conditions to the clinical setting. Currently, placebo-controlled clinical trials test interventions on a background of guideline-recommended therapies that include current "standard of care". Why not follow the same example in the laboratory?

Models in young and healthy animals are good to generate hypothesis, identify mechanistic pathways and act as a general screening for cardioprotection, although their conclusions may not be extrapolated in the context of concomitant co-morbidities and medications, which are at the end unavoidable barriers. It is time to go beyond and establish a second step in the research process using animal models on a background of these factors, considering either patient's co-morbidities and clinical interventions, or even both simultaneously, before going ahead to costly clinical trial.

According to Downey's work, an increasing body of evidence confers P2Y12 receptor inhibitors cardioprotective properties independently of their anti-thrombotic actions[4]. Whereas neither ischaemic pre- nor postconditioning have shown to add further protection when applied in the context of a P2Y12 inhibitor[5], the combination of two other strategies (hypothermia and cariporide) to P2Y12 inhibitors magnified the degree of protection[4], suggesting that there is room not only for incremental protection, but for further translation.

The above discussion only tackles half the issue, i.e. the basic science component. It could equally be argued that clinicians need to establish appropriate selection criteria in their trials to optimise the ability to investigate cardioprotective procedures. While clinicians are concurrently addressing this point, we encourage all translational researchers in this field to reflect on using models that more closely resemble the clinical setting, applying concomitantly the contemporary state-of-the-art therapy to obtain solid results before further clinical study attempts.

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Figure legend.

A sequential approach to translational studies in cardioprotection. (1) The initial reductionist view gives major insight into mechanisms. (2) More clinically relevant animal studies providing less mechanistic insight and some translational value. (3) Proof of concept studies providing limited mechanistic insight but some translational value. (4) Clinical outcomes studies providing no mechanistic value but significant translational importance.