

# Cardioprotective strategies are not “one size fits all”. Is it time to consider personalised medicine?

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Since the discovery of the conditioning phenomenon in 1986 (whereby brief episodes of ischaemia reperfusion protect against a sustained ischaemic insult), thousands of preclinical studies have explored the benefits and signaling mechanisms of this cardioprotective strategy which aims to protect patients undergoing percutaneous coronary interventions (PCI), or cardiopulmonary bypass (CPB) surgery, against ischaemia reperfusion injury. A large number of proof of concept clinical trials have highlighted the benefits of conditioning to protect patients against ischaemia reperfusion injury, but none have yet translated to the clinical routine. The outcomes of the multicenter studies ERICCA,<sup>(1)</sup> RIPHeart<sup>(2)</sup> and CIRCUS<sup>(3)</sup> which involved larger number of patients (1 612, 1 385 and 970 respectively) were eagerly awaited, hoping that pharmacological conditioning with cyclosporine A, or remote ischaemic preconditioning, could soon become part of the clinical routine.

Although these studies repeated protocols that proved to be successful in small clinical trial studies, they all unexpectedly gave a neutral outcome. Cyclosporine A failed to protect patients undergoing PCI and remote ischaemic preconditioning failed to protect patients undergoing CPB. These disappointing outcomes are certainly teaching us a lesson: cardioprotective strategies are not a “one size fits all” strategy. In small proof of concept studies, exclusion criteria (including co-morbidities and co-medication) differ from larger studies. Preclinical studies, and some human proof of concept trials, have clearly highlighted a large number of confounders that may affect the outcome of conditioning including age, co-medication (including anti-platelet therapy, glyceryl trinitrate, anaesthetic agent) co-morbidities (diabetes, hypercholesterolemia) or type of reperfusion.<sup>(4)</sup> It is becoming increasingly clear that the cardioprotective strategy adopted will differ from one patient to the next, function to its characteristics. Further clinical trials testing cardioprotective strategies may therefore have to opt for personalised medicine, adapting the conditioning protocol function to the patient. As an example, recent preclinical studies have highlighted the fact that either ischaemic postconditioning, or cyclosporine A, protected the non-diabetic rat but failed to protect the diabetic animal against ischaemia reperfusion injury.<sup>(5)</sup> A combination of both ischaemic postconditioning and cyclosporine A did not additionally benefit the non-diabetic animals, but it did managed to bring some benefit to the diabetic rats.<sup>(5)</sup> In order that the field moves forward with its objective to see conditioning strategies applied routinely in the clinical setting, it is critical to strengthen translational research: preclinical studies need to better delineate the role of confounding factors in conditioning and clinical studies should consider adapting different strategies on a one to one basis.

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## REFERENCES

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