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REVIEW ARTICLE | OPEN ACCESS

Translating cardiac remote ischemic conditioning for patient benefit - challenges and opportunities

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Acute myocardial infarction (AMI) and heart failure (HF) that often follows are the leading causes of death and disability worldwide. New therapeutic approaches are required to reduce myocardial infarct (MI) size and prevent post-infarct adverse myocardial remodeling, in order to improve health outcomes following AMI. However, the translation of novel cardioprotective therapies, which has been shown to be beneficial in experimental animal studies, into the clinical setting for patient benefit has been very challenging and the results have been hugely disappointing. This failure to translate cardioprotection into the clinical setting has been epitomized by the cardioprotective intervention of remote ischemic conditioning (RIC), which despite showing promise in pre-clinical animal studies and early clinical studies in AMI patients, did not improve clinical outcomes in the large multi-centre CONDI-2/ERIC-PPCI trial. This article will discuss potential strategies for improving the translation of cardioprotection into the clinical setting for patient benefit, and highlight potential opportunities for RIC in cardioprotection. These efforts may help to realize the potential benefits of cardioprotective therapies in improving clinical outcomes following AMI.

Keywords: Remote ischemic conditioning, cardioprotection, acute myocardial infarction, heart failure

Introduction

Acute myocardial infarction (AMI) and the heart failure (HF) that often ensues are among the leading causes of death and disability worldwide. For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI) the treatment priority for limiting myocardial infarct (MI) size and preventing the onset of heart failure (HF) is timely myocardial reperfusion by primary percutaneous coronary intervention (PPCI). Despite a decline in mortality, the number of STEMI patients going onto develop post-infarct HF is on the rise (Schmidt et al., 2012; Szummer et al., 2017). As such, there remains an urgent need to discover novel therapeutic interventions, which can be applied as an adjunct to PPCI to reduce MI size, and prevent post-infarct adverse left ventricular (LV) remodeling. However, the translation of novel cardioprotective strategies or therapies demonstrated to be effective in experimental animal studies into the clinical setting for patient benefit has been extremely challenging and the results have been overwhelmingly disappointing, and this has been the topic of much recent discussion in the literature (Hausenloy et al., 2017; Heusch, 2017; Heusch, 2018; Cour and Lecour, 2019; Heusch and Gersh, 2020; Ho and Ong, 2020).

Ischemic preconditioning (IPC), the ubiquitous endogenous cardioprotective phenomenon in which one or more brief cycles of non-lethal ischemia and reperfusion reduce myocardial infarct (MI) size following lethal acute myocardial ischemia/reperfusion injury (IRI) (Murry et al., 1986), has to be applied prior to IRI. which is not possible in AMI patients. To address this, ischemic postconditioning (IPost) in which intermittent episodes of short-lived ischemia and reperfusion are applied at the onset of reperfusion (Zhao et al., 2003) is performed. IPost is possible in STEMI patients using serial inflations of the angioplasty balloon within the infarct-related coronary artery (Staat et al., 2005) and has been reported to reduce MI size although it did not improve clinical outcomes in STEMI patients treated by PPCI (Engstrom et al., 2017). The failure to translate cardioprotection into the clinical setting has been epitomized by the cardioprotective intervention of remote

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ischemic conditioning (RIC), in which brief cycles of non-lethal ischaemia and reperfusion applied to an organ or tissue (including the arm or leg) remote from the heart, have been shown to reduce MI size in animal models of acute myocardial IRI (Przyklenk et al., 1993; Heusch et al., 2015; Sivaraman et al., 2015; Pickard et al., 2015). Despite showing promising results in pre-clinical animal studies (Przyklenk et al., 1993) and early clinical studies in AMI (Botker et al., 2010; Crimi et al., 2013; White et al., 2015), RIC did not improve clinical outcomes in the large multicenter CONDI-2/ERIC-PPCI trial (Hausenloy et al., 2019).

This article will discuss potential strategies for improving the translation of cardioprotective therapies into the clinical setting and highlight potential opportunities for RIC in cardioprotection.

More rigorous pre-clinical evaluation of novel cardioprotective therapies

One key reason for the failure to realize cardioprotection in the clinical arena has been the lack of rigorous and systematic pre-clinical testing of novel cardioprotective therapies, the consequence of which has been the premature clinical evaluation of treatments with inconsistent and less than robust cardioprotective effects. Potential strategies for ensuring that only the most robust and reproducible novel cardioprotective therapies are tested in clinical studies include establishing guidelines and criteria for pre-clinical evaluation of novel cardioprotective therapies and establishing multicenter research networks for testing of novel cardioprotective therapies.

In this regard, the European Union-CARDIOPROTECTION Cooperation in Science and Technology (COST) Action CA16225, a pan-European research network of leading experts in experimental and clinical cardioprotection, tasked with developing innovative strategies for translating novel cardioprotective therapies into the clinical setting (Andreadou et al., 2018; Hausenloy and Heusch, 2019), aims to address these issues. It has already published practical guidelines to ensure rigor and reproducibility in preclinical cardioprotection studies (Botker et al., 2018), and it will be establishing the IMproving Preclinical Assessment of Cardioprotective Therapies (IMPACT) criteria for improving the preclinical evaluation of novel cardioprotective therapies. Finally, the EU-CARDIOPROTECTION COST Action is currently establishing a research network for pre-clinical multicenter testing of novel cardioprotective therapies. The IMPACT small animal research network is currently being set-up to undertake multicenter evaluation of novel cardioprotective therapies in mice and rat models of acute myocardial ischemia/reperfusion injury (IRI). Validation of the research network will be undertaken using ischemic preconditioning.

Interestingly, the concept of multicenter testing of cardioprotective therapies was first published by Baxter et al (Baxter et al., 2000) who demonstrated that the selective adenosine A1 receptor agonist GR79236 failed to reduce infarct size when administered prior to reperfusion in a multicenter randomized blinded rabbit study. In 2010, with funding from the National Heart, Lung, and Blood Institute (NHLBI), the Consortium for preclinicAl assESsment of cARdioprotective therapies (CAESAR) research network of 3 sites with capabilities of performing acute myocardial IRI studies in mice, rabbits and pigs, was established (Lefer and Bolli, 2011; Schwartz et al., 2011; Jones et al., 2015; Bolli, 2021). The network encompassed the principles of randomization, investigator blinding, a priori sample size determination and exclusion criteria, appropriate statistical analyses, assessment of reproducibility, and core lab analysis of histology and biomarkers. The CAESAR consortium was able to demonstrate cardioprotection with ischemic preconditioning (Jones et al., 2015), but failed to reproduce cardioprotection with other pharmacological agents, such as nitrite (Lefer D et al., 2014), sildenafil (Kukreja R et al., 2014), or chloramphenicol succinate, which had been previously shown to be cardioprotective in single-site studies. Although the consortium is no longer functioning, it illustrates the utility of multicenter network pre-clinical evaluation of novel cardioprotective therapies.

Finally, the CIBERCV (acronym for Spanish network-center for cardiovascular biomedical research) has set up the "Cardioprotection Large Animal Platform" (CIBER-CLAP), a Spanish multicenter network of 5 research centers to perform experimental pig acute myocardial IRI studies testing the efficacy and reproducibility of promising cardioprotective interventions based on a pre-specified design and protocols, centralized randomization, blinding assessment, core lab analyses of CMR imaging, histopathology and proteomics (Rossello et al., 2019). The network is currently being validated using ischemic preconditioning.

Challenges facing the translation of remote ischemic conditioning into patient benefit

The fact that RIC can be easily and non-invasively applied by simply inflating and deflating a pneumatic cuff placed on the upper arm or thigh, has greatly facilitated its testing in AMI patients (Chong et al., 2018). A number of small clinical studies (Botker et al., 2010; Crimi et al., 2013; White et al., 2015) but not all (Verouhis et al., 2016) reported improved myocardial salvage and/or reduced MI size with RIC applied as an adjunct to PPCI in STEMI patients. Furthermore, one follow-up study (Sloth et al., 2014) and a single prospective study (Gaspar et al., 2018) suggested that RIC may even improve clinical outcomes in STEMI. However, the large European multi-center (in Denmark, UK, Spain and Serbia) phase 3 randomized controlled CONDI-2/ERIC-PPCI trial did not find a beneficial effect of RIC on clinical outcomes in STEMI patients treated by PPCI (Hausenloy et al., 2019). The specific reasons for the failure to translate RIC into the clinical setting for patient benefit are not clear, although several potential explanations have been discussed in recent commentaries (Hausenloy et al., 2017; Heusch, 2017; 2018; Cour and Lecour, 2019; Heusch and Gersh, 2020; Ho and Ong, 2020). One potential reason is that the patients recruited into the CONDI2/ERIC-PPCI trial were optimally treated by PPCI and were low-risk as evidenced by the fact that ischemic times were relatively short (median of 3 hours), 96% of patients presented in Killip Class I and cardiac mortality (2.7%) was low at 12 months (Hausenloy and Botker, 2019; Heusch and Gersh, 2020).

Evaluating RIC in higher risk STEMI patients

RIC may be more effective in higher risk STEMI patients such as those presenting with heart failure, cardiogenic shock, or in those who are still treated by thrombolysis as noted in recent commentaries (Hausenloy and Botker, 2019; Botker, 2020). In this regard, a recently published study in which RIC was implemented in the clinical setting as part of a pre- and post-implementation FIRST study reported a potential beneficial effect on major adverse cardiac events in those patients with cardiogenic shock or cardiac arrest (Cheskes et al., 2020). A randomized clinical trial (RIP-HIGH) is being planned to test RIC in patients presenting with heart failure (NCT04844931) and the planned RIC-AFRICA trial (NCT04813159) will evaluate RIC in higher-risk STEMI patients treated by thrombolysis due to limited availability of PPCI (Hausenloy et al., 2020).

In many low- and middle-income developing countries in sub-Saharan Africa, PPCI is still not widely available, and STEMI patients are treated by thrombolysis, resulting in larger infarctions, increased risk of heart failure, and worse clinical

outcomes given that thrombolytic therapy is less effective than PPCI at restoring blood flow to the ischemic myocardium. Clinical studies have reported high in-patient mortality rates in STEMI patients in developing countries in sub-Saharan Africa ranging from 15 to 21% (Bahiru et al., 2018; Varwani et al., 2019) the reasons for which include: prolonged ischemic times (because of limited access to and prolonged transfer time to hospital facilities) (Bahiru et al., 2018; Varwani et al., 2019); high prevalence of comorbidities such as hypertension (present in up to 60% of patients), and diabetes (present in up to 40% of patients) (Bahiru et al., 2018), which in many people remains undiagnosed and untreated (Bahiru et al., 2018); streptokinase thrombolysis is still widely used across the continent to treat STEMI but it is less effective at achieving reperfusion than tissue plasminogen activator; and suboptimal use and compliance with secondary preventative post-STEMI therapy (Bahiru et al., 2018). Importantly, the safety, feasibility, and efficacy of RIC in reducing infarct size in STEMI patients treated by streptokinase thrombolysis has already been demonstrated in the Phase 2 multi-center randomized clinical ERIC-LYSIS trial in the multi-ethnic developing sub-Saharan African country of Mauritius (Yellon et al., 2015). Whether limb RIC can improve clinical outcomes (cardiac death and HF hospitalisation) in this higher-risk STEMI population treated by thrombolysis is not known, and will be tested in the planned RIC-AFRICA Phase 3 randomized clinical trial, which will recruit 1200 STEMI patients treated by thrombolysis across South Africa, Sudan, Uganda, and Kenya (Hausenloy et al., 2020).

Summary and conclusions

Despite intensive efforts over the past 35 years since ischemic preconditioning as a novel endogenous cardioprotective strategy was first described (Murry et al., 1986), the translation of cardioprotection for patient benefit has been elusive (Hausenloy et al., 2016). New strategies are needed to improve the rigor of preclinical evaluation of novel cardioprotective therapies to ensure that only the most robust cardioprotective interventions are tested in the clinical setting. This may be achieved by following guidelines and using criteria that ensure rigor and reproducibility in experimental cardioprotection studies and the establishment of research networks for multicenter preclinical evaluation of novel cardioprotective therapies. Through these collaborative efforts to improve the rigor of pre-clinical evaluation of novel cardioprotective therapies, and testing RIC in higher-risk STEMI patients, the potential to translate cardioprotection for patient benefit may be one step closer.

Acknowledgement

Derek Hausenloy was supported by the British Heart Foundation (CS/14/3/31002), Duke-National University Singapore Medical School, Singapore Ministry of Health's National Medical Research Council under its Clinician Scientist-Senior Investigator scheme (NMRC/CSA-SI/0011/2017) and Collaborative Centre Grant scheme (NMRC/CGAug16C006). This article is based upon work from COST Action EU-CARDIOPROTECTION CA16225 supported by COST (European Cooperation in Science and Technology).

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