Prehospital Emergency Care

ISSN: 1090-3127 (Print) 1545-0066 (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

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**To cite this article:** Andrew Fu Wah Ho & Marcus Eng Hock Ong (2020): Remote Ischemic Conditioning in Acute Myocardial Infarction – Implications of the CONDI-2/ERIC-PPCI Trial for Prehospital and Emergency Medicine, Prehospital Emergency Care, DOI: 10.1080/10903127.2019.1704324

**To link to this article:** https://doi.org/10.1080/10903127.2019.1704324

Published online: 27 Jan 2020.

# Remote Ischemic Conditioning in Acute Myocardial Infarction – Implications of the CONDI-2/ERIC-PPCI Trial for Prehospital and Emergency Medicine

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Abstract

This commentary discusses the findings of the CONDI-2/ERIC-PPCI trial in the context of the existing literature on the topic, and the implications for prehospital and Emergency Medicine in terms of clinical practice and research relating to ischemic conditioning. **Key words:** remote ischemic conditioning; myocardial infarction; CONDI-2/ERIC-PPCI; emergency medical services; emergency medicine

PREHOSPITAL EMERGENCY CARE 2020;00:000–000

Until the recent reporting of the CONDI-2/ERIC-PPCI trial in the Lancet by Hausenloy et al. (1), remote ischemic conditioning (RIC) had been the most promising potential cardioprotective strategy, certainly for prehospital medicine, for improving clinical outcomes in ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PPCI) (2). RIC is the phenomenon that inducing intermittent ischemia and reperfusion in distant tissues (such as by cycling a blood pressure cuff on the arm) can invoke powerful innate protection against ischemic organ injury.

The CONDI-2/ERIC-PPCI trial was well-motivated and intently anticipated by emergency care providers (3, 4). Coronary heart disease is the leading cause of death and disability worldwide, across all country income categories, and have remained so consistently for the past 15 years (5). Timely reperfusion treatment to limit myocardial injury, especially with PPCI, is the cornerstone of STEMI care and has been responsible for the substantial decline in mortality in the past three decades. However, with reperfusion comes ischemia-reperfusion injury, which accounts for substantial infarct sizes (6), leading to an epidemic of heart failure in survivors (7). There is a need to translate cardioprotective strategies to reduce infarct sizes to improve long-term clinical outcomes. In this regard, RIC has seen promising experimental and clinical evidence (8). Amongst these was the CONDI-1 trial (n = 333), where RIC in the ambulance improved myocardial salvage index at 30-days after PPCI (9). At 3.8-year follow-up, the RIC group had 35% fewer major adverse cardiovascular events and 52% reduction in all-cause mortality (10). Similarly, follow-up at 3.6 years of the LIPSIA CONDITIONING trial (n = 696) found that combined RIC and post-conditioning for STEMI reduced MACE and new heart failure (11). More recently, the RIC-STEMI trial (n = 258) found similar results and demonstrated reduced cardiac deaths and hospitalizations at 1-year (12).

Disappointingly, this was not replicated in the real-world. CONDI-2/ERIC-PPCI was a well-executed, adequately-powered, multi-center randomized controlled trial in Europe. More than 5000 STEMI patients treated with PPCI were randomized to either RIC (four cycles of 5-minute inflation/5-minute deflation via an automated cuff device) or to no RIC. RIC was administered either in the ambulance or in the hospital, depending on study site. There was no difference in the primary combined endpoint of cardiac death or heart failure hospitalization at 12 months (9.4% of intervention group and 8.6% of control group, hazards ratio = 1.1; 95% confidence interval, 0.91-1.32). The results remained neutral across subgroups and sites. These results robustly show that

Received October 2, 2019 from SingHealth Duke-NUS Emergency Medicine Academic Clinical Programme, Singapore; Cardiovascular & Metabolic Disorders Program, Duke-National University of Singapore Medical School, Singapore; National Heart Research Institute Singapore, National Heart Centre, Singapore (AFWH); Department of Emergency Medicine, Singapore General Hospital, Singapore; Health Services and Systems Research, Duke-NUS Medical School, Singapore (MEHO). Revision received December 5, 2019; accepted for publication December 6, 2019.

AFWH does not have any conflicts of interest to disclose. MEHO is the principal investigator of an industry-funded study involving a mechanical CPR device; has received grants from Laerdal Medical, grants and personal fees from Zoll Medical Corporation, and non-financial support from Bard Medical and Zoll Medical Corporation; and has a patent method of predicting patient survival licensed to Zoll Medical Corporation, and a patent system and method of determining a risk score for triage pending. AFWH was supported by Khoo Clinical Scholars Programme, Khoo Pilot Award (KP/2019/0034), Duke-NUS Medical School and National Medical Research Council (NMRC/CS_Seedfd/012/2018).

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doi:10.1080/10903127.2019.1704324

RIC, in the form implemented in CONDI-2/ERIC-PPCI, does not improve clinical endpoints.

Aside from the possibility that there is truly no benefit from RIC, which is less likely given consistent experimental and proof-of-concept clinical data, a key explanation for the neutral results is that in emergency care systems where PPCI is standard of care, clinical outcomes are already highly-optimized and overshadows the clinical benefits from adjunct therapies. Secondly, we do not know if the RIC protocol used in the trial, which was empirically chosen, elicited maximum protective signals. If RIC were considered as one would a drug, its dosing, pharmacokinetics, and pharmacodynamics are poorly characterized. The optimal protocol in terms of number of cycles, duration of inflation/deflation, and arm versus leg, still begs clarification. Thirdly, owing to scanty understanding of the mechanism of action of RIC, interaction with comorbidities and co-interventions have been a constant barrier to translation. For example, there is increasing awareness that nitrates (often used in STEMI) may abrogate protection from RIC (13, 14).

CONDI-2/ERIC-PPCI has important implications for prehospital medicine. First, although implemented in some EMS systems, RIC remains not standard of care. Secondly, RIC adds to the list of promising cardioprotective strategies that failed to deliver. Even supplemental oxygen has been dethroned in non-hypoxic STEMI (15). This lends credence to the notion that systems intervention, rather than individual treatments, has the best potential for emergency care systems to improve clinical outcomes in STEMI. In the PPCI era, three-year mortality rates in trial data has reduced from 25% in the 1970s to a mere 6.8% across 11 nations in 2003 (16). It therefore makes sense that cardioprotective interventions often fail to express clinical benefit. In the past few decades, prehospital interventions that have improved outcomes were inevitably those that optimized processes and systems of care from detection, rational triage through to diversion. These include field triage with prehospital 12-lead electrocardiogram transmission (17), diversion to PPCI centers (17), field activation of catheterization laboratories, treatment of out-of-hospital cardiac arrest as they arise (18).

Thirdly, it follows then that there is a potential, but unproven role for RIC in STEMI that receive thrombolysis instead of PPCI due to access issues. This has relevance for EMS in low- and middle-income countries. Indeed, PPCI within the recommend cutoff of 120 minutes (19), is out of reach for the majority of the world population due to both cost and access reasons (20). ERIC-LYSIS, conducted in Maritius, was the only clinical trial of RIC in thrombolyzed STEMI (21). It showed reduced enzymatic infarct size measured by troponin T release. This merits further interrogation in larger clinical trials.

Fourthly, while failing to show effectiveness in STEMI, this does not debunk the effectiveness of RIC in other acute pathologies where EMS has a potential to improve outcomes and where we yet have as good treatment as PPCI: stroke, subarachnoid hemorrhage, traumatic brain injury, hemorrhagic shock, cardiac arrest (3), which are areas of active research.

RIC is cheap, convenient and never been shown to cause harm. It has been successful deployed in both land (9, 22) and air ambulances (23). The large amount of positive experimental and clinical evidence makes it unlikely for them all to be Type I errors. Given these, RIC merit continued attempts for translation to the clinics. Future direction for research should focus on a) optimizing the RIC protocol; b) combination multi-target therapy to enhance the protective signals; c) continued pursuit of the underlying mechanism.

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