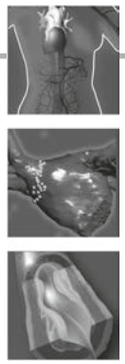

Postconditioning during primary percutaneaous angioplasty: is the jury still out?

"*Despite major therapeutic advances in ST-elevation acute myocardial infarction treatment, adjunctive therapies to reduce reperfusion injury and, ultimately, infarct size are scant in humans.*"

KEYWORDS: infarction ■ ischemia ■ myocardial infarction ■ postconditioning ■ reperfusion

ST-elevation acute myocardial infarction (STEMI) continues to represent a major cause of mortality and morbidity worldwide [1] and infarct size (IS) is a major determinant of prognosis in these patients [2]. Although rapid reperfusion is the mainstay definitive treatment for ischemic myocardium, it may exacerbate the ischemia-related injury (i.e., reperfusion injury) counteracting the benefit of early reperfusion [3]. Despite major therapeutic advances in STEMI treatment, adjunctive therapies to reduce reperfusion injury and, ultimately, IS are scant in humans [3]. In 1986, Murry *et al.* first reported the IS-limiting effect of ischemic preconditioning in a landmark study [4]. In 2003, Zhao *et al.* demonstrated in a dog model that repetitive brief ischemic episodes applied immediately at the onset of reperfusion after a prolonged ischemic insult also can afford cardioprotection, reducing IS and preserving endothelial function similarly to conventional preconditioning, and termed this phenomenon ischemic postconditioning (PostC) [5]. Unlike preconditioning, the experimental design of PostC allows direct application to clinical settings, especially during primary percutaneous coronary interventions. Inflation and deflation of the balloon after reopening the coronary artery can mimic repetitive coronary artery clamping in postconditioned animal models [6]. Notwithstanding, unlike animal models, clinical studies on the prognostic impact of PostC led to conflicting results [7–19].

In 2005, the first studies in humans testing PostC were published by Staat *et al.* [7] and Laskey [8]. Since then, other small clinical randomized trials have found a benefit of PostC on IS reduction [9–13]. However, these studies used release of biomarkers (serum creatinine kinase) or single-proton emission computed tomography as diagnostic tools for detection of IS reduction. To this regard, it is well known that single-proton emission computed tomography is a relatively gross measurement of IS compared with cardiac magnetic resonance (CMR), which has proven to be superior to single-proton emission computed tomography with regard to detection and quantification of myocardial infarction. Moreover, all of these earlier experiences did not stratify the randomization for STEMI location nor related IS to the myocardial area at risk. These adjustments, although not definitive, might be important to reduce bias, in particular when studying a small population.

More recently, five randomized trials assessing the impact of PostC on IS, as assessed by CMR, were published [14–19]. Among them, in the study by Lønborg *et al.*, the absolute IS by CMR (3 months post-STEMI, manual delineation; study primary end point) did not differ significantly between groups and the potential benefit in IS reduction was inferred only after use of the infarct endocardial surface area to estimate the myocardial area at risk, in order to estimate myocardial salvage [14]. Although the authors found a good correlation between this parameter and CMR edema imaging, these data remain unpublished. In 2010, Sörensson *et al.* did not find significant differences between control and PostC groups in IS by CMR performed 6–9 days after index STEMI [15]. In this case, IS was quantified by an automatic CMR algorithm and related to the myocardial area at risk determined by left ventriculography. Freixa *et al.* found that PostC, during percutaneous coronary intervention, did not reduce IS at both early and late follow-up and it might also have a potential harmful effect [17]. In the POST-AMI randomized trial (stratified for STEMI location), we evaluated the effect of PostC on IS in STEMI patients treating all

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cases by percutaneous coronary intervention with direct stenting and intravenous abciximab administration [18]. We found that IS assessed by CMR at 1 month did not significantly differ, but tended to be larger in the PostC group compared with controls both in overall population and subgroups analyses. Thus, collectively the infarct data from the randomized trials of PostC for STEMI does not seem to differ greatly and fails to show a significant impact of PostC on final IS. Moreover, although clinical benefit associated with PostC was suggested by the New York Heart Association class status after 3 months in the Lønborg *et al.* study, there was no significant difference in the Canadian Cardiovascular Society anginal status [14]. Overall major adverse cardiac event rates in the Lønborg *et al.* study did not differ, but only two deaths occurred in the PostC group and these clinical data are also somewhat consistent with the two deaths that occurred in the PostC group in the POST-AMI trial [14]. On the contrary, Thuny *et al.* found, in a small randomized trial enrolling 50 patients, that PostC significantly reduced IS (also after adjustment for risk area) by 38% as assessed both by creatinine kinase-MB and CMR performed at 48–72 h after admission [19]. They found a 32% reduction in myocardial edema at T2-weighted CMR.

> *"...unlike animal models, clinical studies on the prognostic impact of postconditioning led to conflicting results."*

It should be acknowledged, however, that in all these studies, the inclusion/exclusion criteria differed substantially: time from symptom onset >6 h [8–10,13,14,16,17,19], presence of collateral flow to infarct area [9,14,15]; thrombolytic therapy was not always an exclusion criteria [7,9,11,14–17,19] and glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator or they were an exclusion criteria [7–17,19]. Moreover, the PostC protocol was different across studies, being 90 s × 2 (duration of balloon inflation × number of inflations) [8,12], 30 s × 3 [9,10], 30 s × 4 [14,16] and 60 s × 4 in other studies [7,11,13,15,17–19]. Finally, IS evaluation also differed among studies, both in terms of assessment method and of timing adopted for measurements: during the first 72 h [7–9,12,16,19], at 1 week [10,13,15,17], at 1 month [18], at 3 months [14] or at 6 months [11]. For instance, it is important to acknowledge the major contribution of edema to final IS quantification when CMR is performed too early. Another cause for concern with the use of PostC is the integration with a well-accepted therapeutic tool like thrombectomy. To this regard, although thrombectomy could be performed prior to PostC, the few minutes required for its performance during early reperfusion might reduce the potential efficacy of PostC.

> *"...the conflicting results of ... clinical trials bring attention to the need to better understand the mechanisms of postconditioning and the potential conditions under which it may benefit ST-elevation acute myocardial infarction patients..."*

Considering the conflicting results of the available evidence in this field, larger randomized studies will be necessary to better clarify the effect of PostC on IS and on clinical end points before considering ischemic PostC as a new frontier in the treatment of patients with STEMI. We believe that the major limitation around the PostC phenomenon is the extreme complexity of the numerous physiological and biochemical mechanisms responsible for the beneficial effects of PostC in experimental models [20]. Extrapolation of experimental studies to the clinical setting is further complicated by the fact that the optimal window for coupling of PostC to beneficial responses may be substantially shorter than the mean duration of ischemia in typical STEMI patients [21]. In addition, underlying microvascular disease, which is common in STEMI patients (e.g., those with diabetes or left ventricle hypertrophy), may blunt PostC responses. Microvascular injury associated with prolonged periods of ischemia might also be included in this category.

In conclusion, the conflicting results of the previously published clinical trials bring attention to the need to better understand the mechanisms of PostC and the potential conditions under which it may benefit STEMI patients, as well as to potential adverse effects of the treatment, before returning to a final verdict.

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