# Ischemic postconditioning during primary percutaneous coronary interventions—not ready for prime time

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*Provenance:* This is an invited Editorial commissioned by Section Editor Dr. Lei Huang (Cardiac Center of Tianjin Third-Central Hospital, Tianjin, China).

*Comment on:* Engstrøm T, Kelbaek H, Helqvist S, *et al.* Effect of Ischemic Postconditioning During Primary Percutaneous Coronary Intervention for Patients With ST-Segment Elevation Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol 2017;2:490-7.

Submitted Jul 20, 2017. Accepted for publication Jul 22, 2017. doi: 10.21037/jtd.2017.07.116 View this article at: http://dx.doi.org/10.21037/jtd.2017.07.116

In recent years, we have witnessed a remarkable improvement in the care of patients with heart disease. Nevertheless, cardiovascular disease remains the global leading cause of death, with coronary artery disease being the leading cause of cardiovascular death in the US (1). Recognizing that time is muscle, the focus in the care of patients with ST elevation myocardial infarction (STEMI) is based on rapid assessment and transport. Many centers have established regional STEMI programs to ensure timely access to reperfusion therapy including primary PCI whenever feasible. Despite this progress, mechanical or pharmacological restoration of epicardial coronary flow in not always associated with myocardial reperfusion and there is risk of ischemiareperfusion injury (2).

Medications that proved to be beneficial in the setting of acute coronary syndrome such as anti-platelet agents are associated with improved prognosis but their mechanism of action does not involve myocardial protection and they are not specific for STEMI. A few agents tested as myocardial protection substances seemed to have initial promising results that was not confirmed in larger clinical trials (3-6).

The effect of ischemic conditioning as a way of myocardial protection seemed initially promising with many small studies demonstrated dramatic effect. However, as more data is gathered, the benefit of ischemic conditioning seems more controversial (7,8).

The concept if ischemic conditioning is based on the fact that brief episodes of ischemia can protect organs such as the heart from prolonged and potentially lethal ischemia (9). First demonstrated by Murry *et al.* 30 years ago, intermittent occlusions of a coronary artery in dogs reduced the size of infarct when the artery was subject to prolonged ischemia (10). Such an effect was in accord with the observation that when angina episodes precede myocardial infarction the risk of permanent myocardial damage is lower as compared to when the infarction is the first presentation (11).

The mechanism by which ischemic conditioning may protect the heart is complex and include multiple pathways although the precise mechanism is still not fully elucidated (12). Some potential pathways involve mitochondrial  $K_{ATP}$  channels and MPTP (13,14).

Ischemic conditioning can be applied remotely by inducing ischemia to other organ or directly to the arteries supplying the target organ requiring protection. Both methods seem similarly effective (15). Therefore, many studies used remote conditioning. However, in the cardiac catheterization setting, direct ischemia by inflating a balloon in a coronary artery is simple to perform. The concept of ischemic conditioning was first explored as preconditioning, i.e., by applying ischemia prior to the more prolonged ischemic event. However, in the setting of a STEMI, ischemic conditioning can be applied only at a later stage, after the insult has already occurred i.e. ischemic postconditioning. Studies in animal models demonstrated that both are equally effective (16). Still, it seems that the timing of application of ischemic conditioning is important

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in the STEMI setting, and therefore one potential method was applying ischemic conditioning remotely for patients with STEMI en route to hospital prior to reperfusion (17).

Until recently studies assessing ischemic conditioning during STEMI were relatively small (17,18) with some of the more recent studies failing to demonstrate protective effect of postconditioning (19,20). The effects of postconditioning on myocardial reperfusion in patients with ST-segment elevation myocardial infarction (POST) trial was larger, enrolling 700 patients, and failed to demonstrate myocardial reperfusion as assessed by ST segment elevation resolution (21).

The results of the Third Danish Study of Optimal Acute Treatment of Patients With ST Elevation Myocardial Infarction-Ischemic Postconditioning (DANAMI-3iPOST) study were recently published in 7AMA Cardiology and is the focus of this editorial (22). The DANAMI-3 was conducted at the 4 large primary PCI centers in Denmark. The study evaluated 3 different strategies to improve outcome in patients with MI: ischemic conditioning, complete revascularization and deferred stenting. Of 3,854 patients with confirmed STEMI, 1,234 patients were randomized into the ischemic postconditioning study. Patients had to have chest pain onset within 12 hours, ST elevation on ECG of at least 0.1 mV and TIMI grade 0 or 1 on coronary angiography. Initially, TIMI grade 2 or 3 flow was established using a coronary guidewire, a small balloon or thrombectomy. Postconditioning was applied within 60 seconds of establishing flow by inflating a balloon to occlude the coronary artery. The protocol included 4 cycles, 30 seconds each, of occlusion and reperfusion. Stents, mostly drug eluting, were deployed following completion of the postconditioning protocol. The primary endpoint was all cause mortality and heart failure hospitalization, which was different compared to the originally planned primary end point, a composite of cardiac death, reinfarction and heart failure. The two study groups were well matched and technique and medications reflect well the standard practice at the time of the study. The only difference was the higher use of thrombectomy in the conventional arm, although this is unlikely to affect outcome (23). The primary outcome occurred in 11.2% of the conventional arm and 10.5% of the postconditioning arm, P=0.66. There was no significant difference, in all cause or cardiovascular death, hospitalization for heart failure, recurrent MI or target vessel revascularization. No statistical interaction was observed with sub-group analysis. Ejection fraction after 18 months was higher in the ischemic conditioning group,

in patients with anterior MI (45.9% vs. 49.5%, P=0.04), although this did not translate into effect on heart failure hospitalization. A subgroup of 358 patients underwent a sub-study assessing the effect of postconditioning on infarct size by MRI. There was no difference between groups in this sub-study as well. Similarly, there was no effect on ST segment resolution.

The authors should be congratulated for performing this comprehensive study assessing three important questions related to management of patients with STEMI. Although the size of DANAMI-3-iPOST study is not large, it is larger compared to other STEMI studies assessing ischemic conditioning published so far. The primary outcome result in the conventional arm matches the sample size calculations, although one may argue that this study was still underpowered. There are several explanations to the neutral study results.

It is possible that ischemic conditioning might not be effective in humans. This is supported by many recent trials (8,21,24).

The primary endpoint, included heart failure admission, a relatively soft outcome that is driven by physician decision, and mortality. It is unlikely to see a significant difference in mortality with such a small sample size.

It is possible that the target population or technique employed affected the results.

The expected benefit is higher with patients presenting early with anterior MI, and completely occluded artery, i.e., prior to reperfusion. Indeed, patients had to have TIMI 0 or 1, however in this study design all types of MI were included. Patients could be enrolled within 12 hours of symptom onset. There was no difference in sub-group analysis but it may have been beneficial to include only patients presenting early for treatment. However, this would reduce the study size even further, and affect its power. The protocol in DANAMI-3-iPOST included relatively short 30-second balloon occlusions. This may have been not sufficient and such protocol was not well studied previously. Others used longer occlusion duration, or remote ischemia. It is possible that postconditioning following the reperfusion is too late for achieving meaningful myocardial protection and potentially remote conditioning may be employed at an earlier stage.

Overall, the results of DANAMI-3-iPOST do not support routine use of ischemic conditioning during STEMI. This is the first large trial reporting clinical outcomes as opposed to surrogate outcomes in patients with STEMI treated by ischemic conditioning. At this point of time it may be too early to decide that post conditioning post STEMI has failed, but there is not enough information to support its use in clinical practice.

We may need to go back to the drawing board and figure out what is the best way to apply ischemic conditioning, to whom and in what time frame. As most patients with STEMI have good outcome, we may need to identify and target only patients at higher risk for reperfusion injury. Meanwhile, we will need to await the results of other larger studies assessing remote ischemic conditioning, including CONDI2 (NCT01857414) and ERIC-PPCI (NCT02342522).

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Lavi S, Lavi R. Ischemic postconditioning during primary percutaneous coronary interventions—not ready for prime time. J Thorac Dis 2017;9(9):2752-2755. doi: 10.21037/jtd.2017.07.116

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