Postconditioning of ischemic heart by intermittent ventricular pacing at the beginning of reperfusion: novel mechanisms and potential utilities in interventional cardiology settings

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Since the first description of ischemic postconditioning in an in vivo dog model of ischemia-reperfusion (I/R) injury by Dr. Zhi-Qing Zhao and colleagues of Emory University in a seminal paper published in the American Journal of Physiology-Heart and Circulatory Physiology in 2003 (27), this cardioprotective modality has been confirmed in many mammalian species including humans (20) and mice (13, 15, 18, 24) and remains at a focal point of research in the field of cardioprotection. The potential clinical applicability of postconditioning is widely recognized, since it does not require the same pretreatment timing restraint for ischemic preconditioning and could be used during the routine interventional reperfusion procedures, e.g., primary percutaneous coronary intervention (PCI), in the patients with acute myocardial infarction (25).

Ventricular electric pacing-induced postconditioning is a relatively newer modality of postconditioning, which was first discovered and reported in 2006–2007 by Dr. Frits Prinzen and colleagues from Cardiovascular Research Institute Maastricht in The Netherlands (21, 22). The cardioprotective effects are triggered by brief, intermittent mechanical dysssynchrony induced by ventricular pacing at normal heart rate in the very early stage of reperfusion (21, 22). This interesting and practical approach was subsequently confirmed and studied in depth by this extended group of investigators (2–5, 19, 23). In the current issue of American Journal of Physiology-Heart and Circulatory Physiology, Dr. Fawzi Babiker’s group of Kuwait University provides new evidence suggesting a mediator role of the ANG-(1–7)/Mas receptor/nitric oxide pathway in pacing postconditioning (1). This study is a logical extension of the works from these experienced investigators in the field of pacing-induced cardioprotection. Their primary salient finding is the identification of a new role for the ANG-(1–7)/Mas receptor in postconditioning. Despite the fact that cardioprotective effects of ANG-(1–7) have been known for over a decade (9, 10), to our best knowledge, this is the first study to link directly the ANG-(1–7)/Mas receptor to cardioprotection by either ischemic preconditioning or postconditioning (1). These novel findings have broadened our understanding of the mechanisms underlying postconditioning, since the ANG-(1–7)/Mas receptor has not been considered as a key target for myocardial postconditioning (17), whereas adenosine and bradykinin receptors are known to mediate ischemic postconditioning (24).

A few concerns about this study include the lack of measurement of area at risk in determining myocardial infarct size in the rat model of regional I/R. In our opinion, without quantifying the area at risk, there may be uncertainty resulting from variability in positioning and ligating the left anterior descending branch of coronary artery among the rats in various treatment groups. While this methodological deficiency was due to technical limitations presented by the presence of the balloon placement in the isolated rat hearts, the authors acknowledged the importance of normalizing the infarct size data with individual area at risk, as shown in their earlier work in isolated rabbit hearts (5). In addition, it would be interesting to know whether ANG-(1–7)/Mas receptors are also responsible for mediating ischemic postconditioning or whether a unique signaling pathway for pacing postconditioning exists. These issues should be clarified in future studies.

It is noteworthy that while there is mounting evidence for the cardioprotective efficacy of postconditioning in normal individuals of various species (14, 16, 21, 23), the cardioprotective effect of ischemic postconditioning was blunted in aged mice, hypercholesterolemic rabbits, and leptin-deficient obese ob/ob mice (28). The study from our laboratory (28) also reported the inability of ischemic postconditioning to protect type 2 diabetic mice against I/R injury. Until today, there is only one pacing postconditioning study performed in diabetic animals showing that pacing postconditioning failed to protect the ischemic-reperfused hearts isolated from the rabbits with alloxan-induced diabetic conditions (5). Therefore, it is recommended that future preclinical and clinical studies on pacing postconditioning should include animals or patients with chronic comorbidity diseases such as diabetes, hypertension, and hyperlipidemia to rigorously determine the efficacy of pacing postconditioning in these high-risk populations for ischemic heart attack. In fact, the benefits of ANG-(1–7)/Mas receptors have been reported for many of the pathological conditions listed above (6, 7), and thus a vital area of future studies should include assessment of this important peptide in these disease conditions as well.

A critical question remains as to how the pacing-induced postconditioning can be translated into an operational cardioprotective intervention at reperfusion in the real-world PCI settings of interventional cardiology (17). First, the potential clinical utilities and opportunities of pacing-induced postconditioning seem to be very promising, considering that at least four carefully designed clinical trials published from 2012 to 2014 on ischemic postconditioning have yielded disappointing negative results (11, 12, 16, 26). Therefore, it is warranted to further investigate whether ventricular pacing as an alternative postconditioning modality that differs from the graded reperfusion afforded by...
ischemic postconditioning could provide better cardioprotection. Furthermore, pacing postconditioning may circumvent the possible adverse effects of vascular endothelial injury secondary to repeated episodes of balloon inflation and deflation during the ischemic postconditioning procedure. The localized ventricular pacing postconditioning would not have the time delay and potential systemic side-effects that may be caused by pharmacological postconditioning. Until today there is only one clinical trial on pacing postconditioning published by the Prinzen group in 2014 (23). In this randomized, controlled, single-center, single-blinded study, the 60 patients with first ST-segment elevation myocardial infarction (STEMI) were divided into two groups (n = 30/group) that received routine PCI with or without pacing postconditioning using 10 episodes of 30-s right ventricular pacing. Infarct size (~25% smaller, measured with adjusted contrast-enhanced cardiac magnetic resonance) was found in the pacing postconditioning group compared with the PCI alone controls after 4 days, 4 mo, and 1 year of PCI (23). This first trial in human underscored the feasibility to induce cardioprotection with pacing postconditioning during PCI.

Nevertheless, the application of ventricular pacing at the initial stage of reperfusion within the PCI laboratory settings may be practical but may also encounter obstacles and carry potential risks. First, this pacing practice would be in discordance with the currently recommended guidelines for interventional cardiologists on the uses of pacing devices during PCI, such as the one published by the European Society of Cardiology (8). Second, the reported higher incidence of both ventricular fibrillation and atrial fibrillation in the patients undergoing pacing postconditioning intervention (23) raises questions concerning whether the benefits of tissue protection by pacing postconditioning clearly outweigh its possible risk of triggering cardiac arrhythmias that may have lethal consequences in some cases. Third, it is crucial to establish a clearly defined clinical protocol that provides the standardized and optimal duration and algorithm for pacing postconditioning, similar to those tested in the preclinical animal models (5). Taken together, additional well-designed, multicenter clinical trials on pacing postconditioning with long-term clinical outcomes as the primary end points are ultimately needed in supporting the development of this very promising cardioprotective intervention into a clinical reality to reduce I/R injury in the patients suffering myocardial infarction. While the current study of Abawaini et al. (1) revealed the ANG-(1–7)/Mas receptor/nitric oxide pathway as a mediator for pacing postconditioning-induced cardioprotection in rodents, future human studies should explore and validate this new concept in pacing postconditioning as well as other cardioprotective strategies, including the clinically relevant chronic pharmacotherapy with angiotensin-converting enzyme inhibitors, which are known to enhance the plasma levels of ANG-(1–7) (14). However, whether pharmacological induction of ANG-(1–7) by angiotensin-converting enzyme inhibitors given briefly at the onset of reperfusion could mimic the cardioprotective effects of pacing postconditioning remains to be determined.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

F.Y. and L.X. drafted, edited, revised, and approved final version of manuscript.

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