



## Ischemic Preconditioning in Cardiac Cells: from Bench to Bedside

Since 1986 that Dr Charles E. Murry and his colleagues published their discovery about the protective effects of ischemic preconditioning (IPC), a large number of Pro- and Con- studies have been published (1). Besides the protective effects of ischemia itself, a number of pharmaceutical agents may have protective effects against ischemia known as pharmacologic preconditioning. Having a long list of agents, these have been under examinations both clinically and/or in lab setting. Some disease states have been proposed to have a relationship with effects of IPC; including diabetes or high altitude diseases (2, 3). Another variety of IPC is remote IPC which has been acting at remote organ tissues (4-6)

How does IPC with such a wide range of effects work? In fact, IPC works both in cardiac and neurologic cells; two cell types that are highly "ischemia-sensitive"; more interestingly, volatile anesthetics-induced preconditioning (part of a larger phenomenon known as Anesthetic Preconditioning: APC) has protective effects in both cell types; i.e. myocardial cells and brain neurons (7). The underlying mechanisms for IPC and APC are mainly similar; the following items being the most important common mechanisms:

- ATP-sensitive potassium channels in mitochondria ( $mK_{ATP}$ ): being one of the most important mechanisms in both IPC and APC, leads to intracellular protective mechanisms; including but not limited to PKC $\epsilon$  phosphorylation (a subgroup of Protein Kinase C: PKC); among the main mitochondrial related mechanisms, inhibition of mitochondrial permeability transition pore (mPTP) opening, also, " the content of nitric oxide (NO) and also, inhibition of nitric oxide synthase (NOS)" and the role of mitochondrial connexins could not be neglected (7, 8)

- Reactive Oxygen Species (ROS): when mitochondria release small amounts of ROS, both APC and IPC could be triggered, leading to their cardio- and

neuro-protective effects (7, 9, 10)

- Inflammatory cytokines: a cascade of inflammatory cytokines are inhibited due to the protective effects of IPC and APC; mainly through attenuated activity of NF- $\kappa$ B and the downstream of NF- $\kappa$ B-inflammatory cytokines (7, 11-13)

- Apoptosis: increased anti-apoptotic effects of protein Bcl-2, leading to decreased expression of caspase-3 are the main mechanisms considered as IPC effects through inhibition of apoptosis (7, 14-16)

Considering the discovered mechanisms of IPC and APC, it seems reasonable that both cardiomyocytes and brain neurons are benefited from volatile anesthetics-induced preconditioning.

However, the above lines are not the complete picture of IPC and further studies, especially regarding the clinical aspects of the issue are under way. In this issue of the *Journal of Cellular and Molecular Anesthesia*, Anvaripour A, et al. have published their study demonstrating that 4% Sevoflurane could not have a protective effect on myocardial cells as an anesthetic with APC effects (17); a finding in controversy with some of the other previous studies. These results again confirm the delicate path from bench to bedside, which is not always a straight forward one. This time, the path goes through precondition effects of volatile anesthetics.

## References

1. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124-36.
2. Hjortbak MV, Hjort J, Povlsen JA, Jensen RV, Stottrup NB, Laursen MR, et al. Influence of diabetes mellitus duration on the efficacy of ischemic preconditioning in a Zucker diabetic fatty rat model. *PLoS One*. 2018;13(2):e0192981.
3. Paradis-Deschenes P, Joannisse DR, Billaut F. Ischemic Preconditioning Improves Time Trial Performance at Moderate Altitude. *Med Sci Sports Exerc*. 2018;50(3):533-41.

4. Jamshidi F, Entezari S, Alimian M, Siamdoust A, Koleini Z, Mohseni M. Remote ischemic preconditioning in lower limb surgery; the hemodynamic and respiratory effects. *J Cell Mol Anesth.* 2016;1(3):97-102.
5. Talebi Z, Peyvandi H, Dabbagh A. Cellular and molecular mechanisms in perioperative hepatic protection: a review of current interventions. *J Cell Mol Anesth.* 2017;2(2):82-93.
6. Dabbagh A. Remote ischemic preconditioning for noncardiac surgeries: is the final word "ready" yet? *J Cell Mol Anesth.* 2016;1(3):95-6.
7. Chen S, Lotz C, Roewer N, Broscheit JA. Comparison of volatile anesthetic-induced preconditioning in cardiac and cerebral system: molecular mechanisms and clinical aspects. *European journal of medical research.* 2018;23(1):10.
8. Huang YJ, Yuan YJ, Liu YX, Zhang MY, Zhang JG, Wang TC, et al. Nitric Oxide Participates in the Brain Ischemic Tolerance Induced by Intermittent Hypobaric Hypoxia in the Hippocampal CA1 Subfield in Rats. *Neurochemical research.* 2018;43(9):1779-90.
9. Cadenas S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. *Free radical biology & medicine.* 2018;117:76-89.
10. Zhou T, Prather ER, Garrison DE, Zuo L. Interplay between ROS and Antioxidants during Ischemia-Reperfusion Injuries in Cardiac and Skeletal Muscle. *International journal of molecular sciences.* 2018;19(2).
11. Wang PF, Xiong XY, Chen J, Wang YC, Duan W, Yang QW. Function and mechanism of toll-like receptors in cerebral ischemic tolerance: from preconditioning to treatment. *Journal of neuroinflammation.* 2015;12:80.
12. Sheng R, Qin ZH. The divergent roles of autophagy in ischemia and preconditioning. *Acta pharmacologica Sinica.* 2015;36(4):411-20.
13. Kandilis AN, Karidis NP, Kouraklis G, Patsouris E, Vasileiou I, Theocharis S. Proteasome inhibitors: possible novel therapeutic strategy for ischemia-reperfusion injury? Expert opinion on investigational drugs. 2014;23(1):67-80.
14. Wu L, Tan JL, Wang ZH, Chen YX, Gao L, Liu JL, et al. ROS generated during early reperfusion contribute to intermittent hypobaric hypoxia-afforded cardioprotection against postischemia-induced Ca(2+) overload and contractile dysfunction via the JAK2/STAT3 pathway. *J Mol Cell Cardiol.* 2015;81:150-61.
15. Qin HH, Filippi C, Sun S, Lehec S, Dhawan A, Hughes RD. Hypoxic preconditioning potentiates the trophic effects of mesenchymal stem cells on co-cultured human primary hepatocytes. *Stem cell research & therapy.* 2015;6:237.
16. Ordonez AN, Jessick VJ, Clayton CE, Ashley MD, Thompson SJ, Simon RP, et al. Rapid ischemic tolerance induced by adenosine preconditioning results in Bcl-2 interacting mediator of cell death (Bim) degradation by the proteasome. *International journal of physiology, pathophysiology and pharmacology.* 2010;2(1):36-44.
17. Anvaripour A, Shahryari H, Marashian S, Jahangirifard A. The preconditioning effect of sevoflurane on coronary artery bypass surgery patients. *J Cell Mol Anesth.* 2018;3(2):66-73.

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