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About dogs, mice and men: From ischemic preconditioning to anesthetic post-conditioning of the heart

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Coronary heart disease is the single largest killer of American males and females. About every 44 seconds an American will have a new heart attack. About 34 percent of the people who experience a coronary attack in a given year will die from it. Despite better outcomes with early coronary artery reperfusion for the treatment of acute ST-elevation myocardial infarction, morbidity and mortality from MI remain significant, the incidence of congestive heart failure continues to increase, and there is a need to provide a better therapy that reduces the amount of necrosis that may be coupled with better clinical outcome in the setting of MI.[1,2]

In 1986, Murry *et al.* first documented an experimental strategy to reduce acute myocardial infarction, called ‘‘ischemic preconditioning’’ (IP).[3] Utilizing anesthetized dogs, Murry *et al.* demonstrated that brief intermittent periods of myocardial ischemia reduced the size of myocardial infarction resulting from a subsequent total coronary occlusion. The observed protective effect was indeed so powerful that this phenomenon has been described by several investigators as “the strongest form of *in vivo* protection against myocardial ischemic injury other than early reperfusion”.[4] The enthusiasm was in part based on the fact that the phenomenon of ‘preconditioning with ischemia’ could be reproduced in any organ and species, including men.

Analogously to preconditioning, brief episodes of nonlethal ischemia and reperfusion at the onset of reperfusion also reduce myocardial infarct size, known as “ischemic post-conditioning” (POC). And, even ischemic preconditioning of any organ is able to protect another, more distant organ. This mechanism related to IP and POC was coined “remote preconditioning” (RPC). Interestingly, many studies on the search for agents that would be able to mimic those cardio-protective mechanisms, found that volatile anesthetics, which are used every day during surgery, can precondition or post-condition the myocardium against ischemia and infarction as well. Those phenomena were termed the anesthetic-induced pre- or post-conditioning (APC or APOC). Not unexpected, these findings have attracted many anesthesiologists to conduct research studies and to understand the effects of ‘our drugs’ on organ protection.[5,6]

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During the last decades, extensive basic research has elucidated some underlying mechanisms of IP, POC, RPC, APC or APOC and led -in part- to their translation into a clinical setting.[7] In fact, post conditioning or remote preconditioning are currently applied to humans worldwide. This is a very good example that findings at the bench are indeed translated into clinical practice – although it might take 30 years.[7] However, this should not discourage but encourage young scientists to continue research at the bench in order to understand basic mechanisms of clinically relevant observations, such as ischemic preconditioning. In the current issue, Stumpner and colleagues chose a very elegant approach to understand the influence of different cyclooxygenase (COX) inhibitors on the cardio-protective effects of anesthetic-induced post-conditioning, called APOC.[8] Although an important role of COX-2 in PC, POC or APC was found recently, APOC had not been investigated yet.[8] "Inhibitors of cyclooxygenase (COX)-1 and -2 are widely prescribed because of their anti-inflammatory and analgesic properties", as stated by Stumpner et al.[8] In fact, many patients that undergo orthopedic surgery might be on COX-2 inhibition (e.g. Celebrex) prior to surgery which would ultimately lead to the question how this would affect the 'nice' cardio-protective effects of 'our' volatile anesthetics?

While in a large clinical Trial for 'Colorectal Adenoma Prevention' (APC - trial), Celebrex use was associated with an increased cardiovascular risk[9], extensive studies in the perioperative setting have not been performed yet. Nevertheless, application of COX-2 inhibitors are critical in patients with a high cardiovascular risk profile as indicated by mandatory FDA warnings for all COX-2 inhibitors.

Stumpner et al. did not use any of the drugs currently used in a clinical setting but instead used experimental drugs that are highly specific for COX-1 or COX-2 inhibition. In addition, Aspirin as unspecific COX inhibitor was included. While Aspirin (which seems more a COX-1 inhibitor) or COX-1 inhibition did not show any effects on anesthetic induced cardio-protection, specific COX-2 inhibition completely abolished the cardio-protective effects mediated by volatile anesthetics. In light of previous animal studies on COX-2 in the context of preconditioning phenomena, this current study by Stumpner and colleagues emphasizes the fundamental role COX-2 might have in cardio-protection.[8]

As we already know the risk profile of COX-2 inhibitors, these studies come as no surprise and do not necessarily need to be translated from bench to bedside. Furthermore these studies indicate that currently available COX-2 inhibitors should probably still used with caution in patients with a cardiovascular risk profile. Finally, large multi-center studies on currently used COX-2 inhibitors seem warranted to determine how they eventually would affect long term morbidity and mortality after cardiac or non-cardiac surgery.

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