Anesthetic induced cardioprotection: from bench to bedside and retour

Frässdorf, J.

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Chapter 1: General introduction and outline of this thesis

Jan Fräßdorf

In the history of general anesthesia cardiovascular adverse events were apprehended as most anesthetics have negative inotropic effects. However, already back in 1976 Bland and Lowenstein described cardioprotective properties of the volatile anesthetic halothane in animals (1). In 1986 Tarnow et al. (2) demonstrated that isoflurane improves the tolerance to pacing induced ischemia in humans. Kersten et al. (3) suggested in 1997 that isoflurane may induce the strongest endogenous cardioprotection, which is known as preconditioning.

Preconditioning was first described by Murry and co-workers (4). They observed that short, sublethal periods of ischemia prior to a prolonged lethal ischemia reduce infarct size in dogs in vivo. This observation is meanwhile extended to other species (mouse, rat, sheep, human etc.), other organs (gut, brain, liver etc.) and other stimuli (tachycardia, heat, different receptor agonists and anesthetics).

Preconditioning consists of two different time windows: an early phase which begins within a few minutes after the preconditioning stimulus and lasts for 2 to 3 h, and a late phase which occurs 12 to 24 h after the preconditioning stimulus and lasts for 3 to 4 d (5).

Outline of the thesis

This thesis focuses on morphine and anaesthetic induced cardioprotection. In Part I **chapter 2,** an overview on the core topic: Anaesthesia and myocardial ischaemia/reperfusion injury, is given.

Part II of this thesis illustrates morphine's capability to induce cardioprotection.

Opioids are used as analgesics on a regularly basis during surgery. In particular in cardiac surgery a high dose opioid regimen is used to avoid volatile anaesthetics with their known negative inotropic adverse effects. Opioid receptors are indentified as one of the triggers of ischaemic and pharmacological-induced early preconditioning.

Chapter 1 describes a study on late preconditioning by the clinically used opioid receptor agonist morphine. In this *in vivo* investigation, we tested the hypothe-

sis that morphine induces late preconditioning and that opioid receptors and the nuclear transcription factor kappaB are involved in signaling of this cardioprotection.

In **chapter 2** we demonstrated that research is not always straightforward. Aim of the study presented in this chapter was to clarify whether morphine induced preconditioning is mediated by prevention of mitochondrial permeability transition pore (mPTP) opening. However, due to the use of glutamine-containing buffer in our experiments, we initially were not able to induce cardioprotection with morphine in the rat heart in vitro. In contrast, in experiments with a buffer solution without glutamine, we were able to induce morphine induced preconditioning.

Next to mPTP, mitochondrial calcium sensitive potassium channels (BK_{Ca}) were suggested to be end-effectors or mediators of the preconditioning signaling cascade. In **chapter 3** we showed that morphine induced preconditioning is mediated by opening of BK_{Ca} in rat hearts in vitro (in the absence of glutamine in the buffer solution).

Part III of this thesis highlights various aspects of volatile anaesthetic- induced preconditioning.

The objective of **chapter 1** was to determine whether generation of free radicals are involved in isoflurane-induced cardioprotection. By the use of two structurally different antioxidants we demonstrated that free radicals are involved in the signal transduction cascade of isoflurane induced preconditioning in rabbit hearts *in vivo*.

In **chapter 2** we emphasize on the influence of various drugs used in anesthesia (xenon, isoflurane, nitrous oxide and morphine) on tumor necrosis factor (TNF)-alpha induced cellular damage of human umbilical vein endothelial cells (HUVEC).

The noble gas xenon has anaesthetics properties with almost no hemodynamic side effects. Therefore, it could be the ideal anesthetic for patients at risk for cardiovascular events. In **chapter 3** we investigated if xenon can induce late preconditioning and whether cyclooxygenase 2 is required for this protective effect. We could clearly demonstrate that the inert noble gas xenon induces

late preconditioning and that cyclooxygenase 2 is involved in the signaling of this cardioprotection.

Almost every inhalational anaesthetic does have some cardioprotective properties. However, in **chapter 4** we describe that nitrous oxide does not induce cardioprotection.

Part IV of this thesis conveys reports illustrating the transfer of our pre-clinical experimental data into the clinical setting.

Chapter 1 shows for the first time that the concept of volatile anaesthetic induced preconditioning is effective in humans undergoing coronary artery bypass grafting. This effect seems to depend on the employed preconditioning protocol and other medication given during the operation.

Part V of this thesis addresses the question why most of the clinical trials failed to show cardioprotection induced by preconditioning.

Early research on preconditioning was done in healthy young animals. **Chapter 1** shows that regulation of mitochondrial respiration is age dependent. These results could explain why in the clinical setting it is difficult to induce preconditioning.

Diabetes mellitus can abolish cardioprotection induced by preconditioning. In **Chapter 2** we report on the exact level of the preconditioning signaling cascade at which this blockade occurs.

Going back from bedside to bench again we investigated in **chapter 3** whether the clinically used preconditioning protocol or the antifibrinolytic agent aprotinin could be responsible for the observed differences in the results between our clinical trial illustrated in **chapter 1 of part IV** and other clinical trials that were unable to induce preconditioning in humans.

References

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