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The Effects of Sevoflurane on Cardiac Function of the Rat in the first 24 hours after Resuscitation

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Cardiac arrest and post-resuscitation period continues to be a major health problem. Around half of the victims suffering from cardiac arrest are initially resuscitated, but a minority of them survives to hospital discharge. One of the most common causes of death following resuscitation has been shown to be refractory myocardial damage. So far, there are few pharmacological therapeutic options to improve the prognosis of post-resuscitation myocardial dysfunction.

One possible protective option is ischaemic preconditioning with multiple brief ischaemic episodes protecting the heart from a subsequent sustained ischaemic insult. Besides this, there are other preconditioning stimuli that result in similar protection, e.g. the application of volatile anaesthetics including Sevoflurane. In addition to the preconditioning effect, the term "postconditioning" was recently introduced for interventions after ischaemia. Also, volatile anaesthetics have cardioprotective effects when administered during reperfusion.

Previous studies have investigated the effects of volatile anaesthetics only in regional myocardial ischaemia or in isolated hearts. Most of these studies used only one anaesthetic concentration and one time of application. In the present study, it was investigated for the first time if Sevoflurane is able to provide cardiac protection in an *in vivo* rat model of global ischaemia in the first 24 hours after resuscitation. Also, the concentration dependence was analysed and it was investigated, what time of application (30 min before, during, 30 min after resuscitation) provides the optimal cardioprotective effect.

An *in vivo* model of cardiac arrest and resuscitation was used. All animals received a 5-minute application of Sevoflurane in different concentrations (1 MAC, 0.5 MAC, 0.25 MAC) and at different points of time (30 min before, during or 30 min after resuscitation). Cardiac arrest was induced using electrical fibrillation; after 6 minutes, the animals were resuscitated mechanically and pharmacologically. To measure cardiac function, a left ventricular pressure-volume conductance catheter for rats was used.

The evaluation of cardiac parameters 24 hours after resuscitation showed significant positive effects of Sevoflurane on myocardial function.

Sevoflurane administrated before resuscitation had the most beneficial effects on the cardiac function with a concentration corresponding to 1 MAC of Sevoflurane being most protective. Anaesthetic preconditioning is known to improve the recovery of contractile function after ischaemia. There are only very few preceding studies having investigated whether preconditioning with Sevoflurane is dose related, but they indicate that Sevoflurane is maximal cardioprotective at a concentration of 1 MAC.

An application of Sevoflurane during resuscitation had slight positive effects on certain parameters. Yet, this time of application was with regard to the cardiac function 24 hours after resuscitation worse than the application before or after resuscitation. It has been shown earlier, that volatile anaesthetics reduce myocardial oxygen demand during ischaemia and thereby reduce myocardial damage. The overall impact of application during ischaemia still seems relatively small when compared to the preconditioning effect or the effect on reperfusion injury and postconditioning. In the present study for an SDR administration, the smallest dose corresponding to 0.25 MAC of Sevoflurane was most protective. These results with the least dose having the best cardiac outcome can be explained by the haemodynamic side effects of volatile anaesthetics which may be disadvantageous in the situation after resuscitation.

When Sevoflurane was administrated in the reperfusion period, there was a positive effect on the cardiac function. It is known that the cardioprotective pathways of volatile anaesthetics can also be activated during the reperfusion period. With regards to the time of administration, the present results point towards a better effect of preconditioning than postconditioning on cardiac functionality. This phenomenon has already been observed. Like in the groups receiving SBR, there was a dose-dependent effect with a higher dose of 1 MAC being the best. So far there are no studies investigating the cardiac protective effect of lower doses of Sevoflurane in the reperfusion period.

Concludingly, Sevoflurane may provide cardiac protection in the peri-resuscitation period. The present results indicate towards a positive effect of Sevoflurane given before or after resuscitation with a dose-dependent effect and 1 MAC being the most protective. An application during resuscitation seems not as beneficial and if so, animals benefited from a rather low dose (0.25 MAC).

The results of the present study are very promising. Yet, there is the need for more experimental work and clinical trials to better understand relevant mechanisms of post-

resuscitation myocardial dysfunction and the possible impacts of pre- and postconditioning with Sevoflurane upon it.