

# Anaesthetic agents and the heart

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Anaesthesiologists administer agents on a daily basis to patients without consideration of how these agents potentially affect the heart. This article seeks to summarily describe effects of anaesthetic agents on the heart.

**Keywords:** anaesthetic agents, heart

## Introduction

Anaesthesiologists administer agents daily to patients necessitating consideration of how these agents potentially affect the heart. This article seeks to summarise literature on effects of anaesthetic agents on the heart commencing from animal studies to clinical trials.

## Induction agents

Propofol, with structural similarities to phenol-based free radical scavengers, has been found to attenuate free radical-mediated lipid peroxidation and systemic inflammation in patients with impaired myocardial function.<sup>1,2</sup> Propofol acts in a similar mechanism to the endogenous antioxidant vitamin E to scavenge reactive oxygen species.<sup>2,3</sup> However, propofol concentrations used in animal studies showing cardio-protection, were at doses 10 times more than the clinical range.<sup>1</sup>

Ketamine provides haemodynamic stability by preserving cardiac output through central nervous system stimulation and prevention of catecholamine reuptake in neurons. Ketamine attenuates the increase in IL-6, IL-8 and TNF- $\alpha$  and therefore reduces the pro-inflammatory arm of the stress response. This suppressive effect on the inflammatory cascade may confer organ protective benefits. After CABG on CPB, ketamine was found to attenuate neutrophil activation and decrease IL-6 levels when compared with a placebo.<sup>1,4-6</sup> Ketamine inhibits neutrophil adhesion during reperfusion at clinically relevant doses.<sup>1</sup>

Midazolam and thiopentone were found to effect their anti-inflammatory activity through inhibition of neutrophil function in an in vivo investigation.<sup>7</sup> Midazolam was also shown to significantly inhibit "lipopolysaccharide-induced up-regulation of pro-inflammatory mediators and activation of mitogen-activated protein kinase"<sup>8</sup> Nuclear factor- $\kappa\beta$  transcriptional activity was also suppressed. An animal study by Bartosikova et al. showed improved post-ischaemic recovery in hearts of rats pre-treated with midazolam 0.5 mg/kg intraperitoneally.<sup>9</sup>

Morphine elicits immunomodulatory actions on lymphocytes, granulocytes and macrophages. There is also evidence of morphine's reduction in myocardial ischaemic size. Fentanyl

has a diminished ability to attenuate the inflammatory response. Midazolam has little influence on the body's defence systems.<sup>1,2,10</sup> Kato and Foex<sup>1</sup>, in a review of predominantly animal studies investigating myocardial protection effects of opioid anaesthetics, reported that only morphine concentrations used experimentally were achievable in clinical scenarios (3 mg/kg).

## Alpha-2 agonists and myocardial protection in cardiac surgery

Before the era of dexmedetomidine, several studies investigated the effects of clonidine, an  $\alpha$ -2 agonist, on myocardial protection. The results of the effects of clonidine on myocardial protection show inconclusive evidence.

Helbo-Hansen et al.,<sup>16</sup> in 1986 examined forty patients undergoing CABG surgery, twenty of whom received decremental doses of clonidine while the other 20 were controls. They found that plasma adrenaline and noradrenaline levels were less than one-third of the control group in the clonidine group, 90 minutes postoperatively. In 1993, Dorman et al.<sup>17</sup> found reduced adrenaline and noradrenaline levels post sternotomy in the clonidine group, but patients experienced much lower systolic blood pressures and more patients needed pacing in this group. Aortic cross-clamp (Aocx) time was coincidentally shorter in the group that received clonidine.

Abi-Jaoude et al.<sup>18</sup> performed a randomised controlled trial (RCT) of 24 patients looking at haemodynamic effects of clonidine premedication and found that it conferred an unstable haemodynamic status requiring higher doses of vasoactive agents. Myles et al.<sup>19</sup> also found clonidine to lead to more hypotension and bradycardia, despite the improvement in some aspects of quality-of-life parameters.

In 1999, Loick et al.,<sup>20</sup> in an RCT of 70 patients, compared intravenous clonidine with high thoracic epidural anaesthesia (TEA) and placebo. They assessed troponin as a marker of myocardial ischaemia. An assessment of laboratory parameters was made at baseline, 30 minutes, 12 and 24 hours postoperatively. An increase in troponin levels was observed in the first 24 hours in all groups, but less so in the clonidine than the control group,

although much higher than the TEA group. The only mortality in the study was in the clonidine group. Clonidine did not cause a significant attenuation of plasma epinephrine release. It was found to lead to adverse haemodynamic events.<sup>21,22</sup>

Dexmedetomidine is a pharmacologically active S-enantiomer of medetomidine with a high affinity for  $\alpha$ -2 adrenoreceptors at an  $\alpha$ -2: $\alpha$ -1 ratio of 1600:1.<sup>21,23</sup> It has a molecular weight of 236.7 Dalton and is chemically described as (+)-4-(S)-1H-imidazole monohydrochloride.<sup>23,24</sup>

Dexmedetomidine can prevent changes in cardiac contractility, ejection fraction, stroke volume and calculated systemic vascular resistance.<sup>2,25,26</sup> At doses lower than 0.4  $\mu$ g/kg/hr, it has been shown to have minimal haemodynamic adverse effects.<sup>26</sup> It is proven to reduce the release of endogenous epinephrine and norepinephrine levels perioperatively.<sup>25,26</sup> In a study of 80 CABG patients, Jalonen et al.<sup>27</sup> found a 90% decrease in plasma concentrations of norepinephrine in patients who received dexmedetomidine.

In preclinical studies, dexmedetomidine was shown to decrease the central sympathetic outflow with decreased plasma catecholamines.<sup>28</sup> This resulted in a decrease in cardiac output per index, heart rate, and an increase in left ventricular end-diastolic pressure (LVEDP). Systemic vascular resistance index (SVRI) increased, and the rate of rise of left ventricular pressure ( $dP/dt_{max}$ ) declined initially, and then stabilised. Systemic and trans-coronary oxygen extraction increased, reflected by decreased mixed venous oxygen saturation at similar arterial oxygen content. There was vasoconstriction of the resistance, and not of the conductance coronary vasculature due to stimulation of cardiac sympathetic nerves.

Pre-ischaemic dexmedetomidine administration has been shown to reduce infarct size more significantly with a higher dose. This phenomenon was postulated to be due to ischaemia preconditioning effect.<sup>29</sup> Consequently, post-ischaemia dexmedetomidine administration was seen to worsen the infarct size compared with control.<sup>30</sup> Dexmedetomidine preserves blood flow in the mid- and endocardial compared with epicardial layers of the myocardial, in the face of coronary artery stenosis or ischaemia, resembling a "reverse steal" phenomenon.<sup>31</sup> A 25-minute period of dexmedetomidine preconditioning stimulated pro-survival kinases, reduces myocardial infarct size, and improves recovery.<sup>32</sup>

In humans, levels of noradrenaline immediately, and 12 hours post-surgery, were significantly lower in the dexmedetomidine compared to a control group.<sup>33</sup> Inflammation is a significant contributor to perioperative morbidity. Administration of dexmedetomidine attenuated the increase in cytokine release.<sup>34</sup> It significantly decreases IL-6, IL-8 and TNF- $\alpha$  immediately after surgery.<sup>35</sup>

## Volatile agents

Kato and Foex,<sup>1</sup> in a review of studies predominantly in animals, using volatile and intravenous anaesthetics, made the following observations:

- the cardioprotective effects conferred by halogenated agents were in concentrations similar to those used in clinical practice 0.5–2.0 mean alveolar concentration (MAC);
- of the opioid anaesthetics, only morphine concentrations used experimentally were achievable in clinical scenarios (3 mg/kg);
- neutrophil adhesion during reperfusion was inhibited by ketamine at clinically relevant doses;
- propofol concentrations used in animal studies showing cardioprotection, were at doses 10 times more than the clinical range; and
- volatile anaesthetic agents conferred myocardial protection when compared with non-volatile anaesthetic agents in patients undergoing CABG and OPCAB.<sup>11</sup>

Symons and Myles<sup>12</sup> had looked at myocardial protection with volatile anaesthetic agents during CABG surgery in a meta-analysis of 27 studies with 2 979 patients included. Their endpoints included myocardial ischaemia, myocardial infarction, mortality, cTnI concentrations, inotropic support, cardiac index and length of ICU and hospital stay.

Only five studies had reported on mortality, 12 on MI and eight on myocardial ischaemia.<sup>12</sup> No significant differences were found in respect of MI, myocardial ischaemia, mortality, and length of ICU stay. However, those who received volatile agents had significantly lower Troponin I concentrations compared with those who did not. They also had 20% higher cardiac indices, lesser inotropic support requirements and shorter hospital stays. This study included trials from 1985 to 2005.

The cardioprotective properties of volatile anaesthetics have been attributed to preconditioning.<sup>13,14</sup> Sevoflurane is said to elicit changes in the mitochondrial proteins involved in energetic metabolism.<sup>13,14</sup> The positive results of myocardial preconditioning are supported by a meta-analysis of experimental animal studies by Kunst et al.<sup>2</sup>

Looking back to earlier studies (1966–2005), Yu and Beattie<sup>15</sup> analysed data from 32 studies with 2 841 patients. They, too, did not find a significant reduction in mortality rate in the 10 studies that reported on it. They did, however, find a reduction in the rate of MI with sevoflurane and desflurane. Of concern was a finding of an increase in the rate of MI with enflurane that they found in a post hoc analysis. Sevoflurane and desflurane were also found to be associated with significant reductions in cTnI. It would seem from this meta-analysis that not all volatile agents are cardioprotective, but that enflurane may, in fact, increase the rate of MI.<sup>15</sup>

In a recent systematic review of the literature, which was followed by a consensus-based voting process, volatile agents amongst all anaesthetic agents were selected as contributing

towards lower mortality in cardiac surgery.<sup>36</sup> They reported on interventions with a statistically significant effect on mortality in the setting of cardiac surgery through a systematic Medline/PubMed search and contacts with experts, and it was voted on by clinicians around the world.

### Anaesthesia adjuvants

Kim et al.<sup>37</sup> reported a reduction in postoperative ischaemic markers with lignocaine compared to control. Systemic lidocaine in an infusion of 2 mg/kg/hr has also been shown to protect against myocardial ischaemia and reperfusion injury after OPCAB.<sup>38</sup> However, it was not shown to reduce the inflammatory response. Antioxidants, calcium-channel blockers, and magnesium reduce the incidence of ventricular arrhythmias and enhance myocardial recovery.<sup>22,39-43</sup>

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