Cardiovascular aspects of anaesthetic agents

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Introduction

When contemplating the anaesthetic management of any patient, safety is paramount. An important aim, therefore, is to maintain an optimal circulation and utilise pharmacological or other treatment to protect the cardiovascular system during the perioperative period. It is also important to acknowledge, understand and anticipate the cardiovascular actions of the anaesthetic agents that are selected to provide anaesthesia. This review will focus on anaesthetic drug actions that can be potentially favourable or threatening to the circulation. The anaesthetist should not only be confident to deal with the expected consequences of the agents used, but also be prepared for drug responses that are exaggerated and potentially dangerous. Some aspects of anaesthetic drugs assist the circulation and may even offer protection to vital organ function, including the circulatory system: This review aims to provide the background and an update on the developments in this aspect of anaesthetic care.

The pre-operative visit allows us to assess the patient’s circulatory status, circulatory reserve and capacity to mount a cardiovascular response in the pre-anaesthetic period. We can form a clinical understanding of the patient’s general functional capacity, although ideally, if we had the information available, we may want to know greater detail concerning cardiac filling, contractile status, vascular tone (both arterial and venous), arterial system ‘stiffness’ or impedance, and possibly, other things too! Information derived from these baseline parameters will, for example, help us understand the underlying mechanisms causing the patient’s blood pressure to deviate from normal limits and guide us where we need to intervene.

At the time of surgery the responses observed in the cardiovascular system are intimately related to the way in which anaesthetic agents are employed allied to the function and status of the patient’s autonomic nervous system and other circulatory reflexes. We need to have insight into the autonomic nervous system (ANS) status for our patient. If a patient has impaired pre-operative circulatory status and regulation (heart failure, both primary and secondary, or significantly decreased blood volume), this is linked to heightened autonomic nervous system activity mediated primarily through sympathetic nervous system expression. In this case, maintenance of an adequate circulation may be dependent on maximal uninterrupted ANS activity. Where a drug exhibits strong ANS depression, this might cause an exaggerated response. Alternatively, if a patient has a chronic illness that leads to blunting of autonomic circulatory reflexes, (either afferent, central processing or efferent blunting), then understanding this would help us to anticipate that this patient may not manifest reflex responses in the usual way when challenged with usual situations expected to initiate baroreflex activity.

Where a patient has impaired cardiac performance with limited reserve, we must ensure the anaesthetic is delivered so as to confer minimal or no cardiac depressive effects. If a patient experiences an acute illness with results in impaired vascular smooth muscle performance or hypo-responsiveness (both resting and maximal performance), as is often the case associated with sepsis, then we must re-adjust our expectations of the relation between blood volume, vascular tone and venous return to the heart. Where a patient has impaired general vascular tone, and compromised venous return to the heart, then seemingly mild vasodilatory effects of anaesthetic agents can lead to an important potentially dangerous reduction in cardiac preload and hence cardiac output.

In health, vital organs, including the heart, usually exhibit a close coupling of local parenchymal metabolic activity to local vascular tone, particularly within certain blood pressure ranges. In the case of ischaemic heart disease and coronary stenosis, there may be a local environment that results in greater than normal vasodilation which has the effect of enhancing collateral circulation to a region of myocardium beyond the stenosis or flow limitation. These areas can thus be adapted to reflect usual resting conditions so that the patient’s myocardium is not ischaemic and the patient is asymptomatic. However when the patient is subjected to anaesthesia and surgery these conditions can change, either inducing demands for more activity and coronary flow to an area of myocardium distal to a stenosis, or alternatively, by being subjected to a treatment/anaesthetic drug with a potent vasodilatory effect, leading to lower coronary perfusion pressure and, possibly, lower coronary blood flow. These are situations to which we are frequently exposed.
Intravenous anaesthetic agents

The most commonly used anaesthetic induction agents are propofol and thiopental.

Propofol

At doses of propofol that can reliably induce complete lack of awareness (hypnosis), this invariably causes a decrease in blood pressure [1]. This can be more prominent in elderly patients. The onset of both hypnotic and cardiovascular effects is rapid (peak response achieved at well less than 2 minutes), and coincides with loss of EEG amplitude. A dose of 2-2.5 mg/kg predictably produces a decrease in blood pressure, even in healthy patients. There is both a reduction in cardiac output and arterial vascular resistance associated with a proportional decrease in blood pressure, indicating that the haemodynamic effect of propofol leads to both decreased venous return and a generalised lowering of vascular tone (vasodilation) [2]. Propofol has been shown, at least experimentally, to have a dose-dependent negative effect on myocardial contractile function, though to what extent this is a direct effect, rather than an effect of propofol on the central ANS, particularly leading to decreased sympathetic nervous system activity, is not clear.

Propofol may cause an increase in heart rate when hypotension occurs, though it is recognized that baroreflex and sympathetic nervous system activity is blunted. Propofol, despite potent vasodilatory effects, has been shown to lead to similarly proportional decreases in myocardial metabolism and coronary perfusion, so that while alterations in coronary perfusion may lead to inadequate regional substrate delivery in patients with coronary artery stenoses, propofol usually can be administered in moderate doses without causing myocardial ischaemia [1]. Propofol has not been shown to have direct cardioprotective effects. Propofol is generally avoided in head injured patients with intracranial hypertension, because of concerns associated with cerebral vasodilatory effects which could potentially exacerbate intracranial pressure problems.

Barbiturates

Thiopental and methohexital have been used as induction agent for many years. They have predictable hypnotic effects with rapid onset, and a pharmacokinetic profile that includes rapid redistribution between body compartments that leads to a short duration of action. Cardiovascular depression is an important and predictable side effect of barbiturate induction agents. Barbiturates act on the circulation both through central nervous system (ANS) depression as well as direct cardiovascular effects [3]. The most prominent effect is vasodilation, though thiopental is known to have a direct myocardial depressant. Thus induction of anaesthesia with barbiturate drugs decreases cardiac output due to a combination of central and peripheral (direct and indirect) cardiovascular effects. During induction with pentothal in healthy patients, moderate baroreflex-mediated tachycardia may be observed. Myocardial oxygen consumption increases are matched with an increase in coronary blood flow. However, patients with significant coronary artery disease, require careful use of barbiturates to maintain an adequate coronary perfusion pressure. Thiopental-induced vasodilation has been long recognized to be potentially dangerous in patients with hypovolaemia when the patient is dependent on intact cardiovascular reflexes to maintain adequate vital organ perfusion. Barbiturates (and propofol) have been demonstrated to prolong Q-T interval, and therefore may not be ideal induction agents for patients with known Q-T prolongation or related dysrhythmias.

Benzodiazepines

Benzodiazepines have relatively small circulatory effects when compared with other intravenous anaesthetic agents. When used as sedative or induction agents, peak hypnotic and cardiovascular effects occur after some minutes. Only modest reductions in blood pressure are thought to occur due to the mild effects on both vascular tone and baroreflex activity. Benzodiazepines have been recognized as providing relatively minimal haemodynamic perturbation at the time of induction and have been used to advantage in patients with ischaemic heart disease [4]. The stimulation and pain associated with airway instrumentation or surgery is not blocked by benzodiazepines. Therefore in order to minimize the adrenergic response to these stimuli, other analgesic agents must be combined with benzodiazepines to avoid tachycardia or hypertension. Notably, benzodiazepines in combination with opiates have synergistic effects, resulting in a greater blood pressure reduction than might have been expected by just a summation of the usual effects of each drug by itself. This is thought to occur through a potent reduction in sympathetic nervous system activity which leads to more than expected vasodilatation and venous blood pooling.
Ketamine

Ketamine is a potent analgesic drug used to produce unconsciousness at higher doses. It is often chosen as an anaesthetic agent because of its cardiovascular and respiratory profile. Ketamine has minimal effects on respiratory function, and has an apparently stimulatory effect on cardiovascular function, which makes it advantageous in situations where cardiovascular function is compromised, and where spontaneous ventilation might be desired. The mechanisms of action for ketamine are still not completely understood, and the anaesthetic effect is described as ‘dissociative’ rather than hypnotic. Ketamine’s cardiovascular effects are attributable to its central stimulatory effects which in turn are the result of a central dis-inhibition leading to activation of the sympathetic nervous system mediated, at least in part, through release of norepinephrine. The net effect of a sustained or augmented sympathetic nervous system has made ketamine popular as an analgesic and induction agent where there is a requirement not to depress adrenergic-mediated circulatory effects [5]. Ketamine does have direct effects on the cardiovascular system, including dose-dependent myocardial depression, though this is not observed clinically when the activity of the central ANS is maintained [6]. Ketamine-related increases in cardiovascular performance are completely mitigated when ketamine is combined with other intravenous anaesthetic agents, including benzodiazepines or opiates. Ketamine’s effect may be more pronounced on the pulmonary circulation [7], therefore, care must be taken if pulmonary hypertension or right heart dysfunction is present. Ketamine is often used for co-induction of anaesthesia with other agents, e.g. thiopental, in order to induce anaesthesia without inducing the negative circulatory effects that would occur with sole use of thiopental at its usual dose. Ketamine and NMDA receptor agonism may be beneficial in terms of its analgesic action and experimental animals models suggest it is possibly even neuroprotective, leading to the more common use of either racemic ketamine perioperatively, or, especially the ketamine S+ isomer. On the other hand, ketamine has also been shown in animal models to block some forms of cardiac protective mechanisms. This effect may be specific to one of the isomers, though this has not been texted clinically.

Dexmedetomidine

The cardiovascular effects of α-2 agonists (clonidine and dexmedetomidine) have been well recognized as having 2 phases. At lower doses, they have predominantly central depressant effects on sympathetic nervous system activity, leading to lower blood pressure (vascular tone), lower heart rate, lower myocardial performance, and lower cardiac output as a result of reduced venous return and decreased myocardial contractility [8,9]. When dexmedetomidine is injected rapidly, there can be a transient increase in blood pressure together with a reflex decrease in heart rate, related to direct α-2 receptor mediated peripheral vasoconstriction. The central sympatholytic effects and falls in blood pressure and heart rate are dose-dependent and can be profound, which is why dexmedetomidine should be administered slowly and in moderate doses. Alpha-2 agonists have been shown to reduce the incidence of myocardial ischaemia when administered perioperatively [10].

Opioids

Opioid receptors are found widely in the central and peripheral nervous systems as well as in other organs associated with the cardiovascular system. Therefore opiate administration has both direct and indirect effects on the circulation. A close relationship between pain regulation and cardiovascular systems has long been recognized. Control of the cardiovascular system by the ANS function, including neurohumoral regulation of cardiovascular function, occurs in the brainstem. Similarly, opioids, including mu agonists which are commonly administered to patients perioperatively, act primarily in the central nervous system including in the brainstem. Perioperatively, the main circulatory effects of opioid administration are a reduction in blood pressure and heart rate. High doses of opioids can depress the baroreceptor reflex. Morphine is known to cause histamine release, though the mechanism that causes this is independent of mu opioid receptors activation. Opioids have been reported to have direct effects on heart muscle function although the results are inconclusive. Meperidine (pethidine), an opioid with activity at kappa and mu receptors with prominent atropine-like side-effects, has been shown to be able to influence noradrenaline release in sympathetic nerve fibres in the heart in one model.

Opiate receptors are involved in many aspects of signal transduction including participation in the mediation of some forms of intrinsic protective responses in heart tissue during impending infarction associated with prolonged ischaemia [11,12]. Administration of opioids can have similar effects to potent inhaled anaesthetics as far as conferring or mediating some degree of myocardial protection in the event of ensuing prolonged myocardial ischaemia, and it is clear that there are common aspects in the signalling and transduction of this protective effect [13,14].
Inhalational anaesthetics

Potent inhalational anaesthetic agents depress myocardial contractility in both healthy and compromised hearts [15]. There is a minimal difference in the degree of myocardial depression when comparing the modern potent inhaled agents (isoflurane, desflurane, sevoflurane), but all appear to be cause less myocardial depression compared with halothane. Myocardial relaxation may be slowed by potent inhaled anaesthetics, and diastolic ventricular stiffness also typically increases with more potent inhaled anaesthetic administration.

With regards to coupling of the left ventricle and the arterial system, potent inhaled anaesthetics appear to have minimal effects at low concentrations. In contrast, at higher concentrations (in experimental conditions) greater depression of ventricular contractility occurs relative to arterial vasodilation, leading to less mechanical efficiency and reduced blood flow.

As far as general circulatory parameters, blunting of baroreflex activity and negative chronotropy occurs with all potent inhalational agents, although to a lesser extend compared to halothane. There is consistently decreased blood pressure, to a large extent related to anaesthetic vasodilation effects and decreased ventricular afterload, as well as modest anaesthetic negative inotropic effects. There can also be vagally mediated circulatory effects related to noxious airway stimulation from potent inhaled anaesthetics which are administered in rapidly increased inspiratory concentrations.

Potent inhaled agents generally slow cardiac conduction in a dose-dependent fashion, including prolongation of the Q-T interval, though dramatic disturbances in conduction such as bradycardia or atrioventricular block are seldom observed with modern potent inhaled anaesthetics [16]. A relation between potent inhaled anaesthetic agents and epinephrine-induced dysrhythmias has been recognized for many years. Regulation of coronary vascular resistance is the main effector by which coronary blood flow is distributed and delivery of substrates is matched to local myocardial need. All the potent inhaled anaesthetic agents have vasodilatory properties that blunt coronary ‘autoregulation’, which can lead to perfusion which exceeds local demand for delivery of substrates. Coronary ‘steal’ was described for the situation where regional myocardial ischaemia could occur in the setting of vasodilatory effects of a potent inhaled anaesthetic agent. In theory, when high grade coronary occlusion is present, the corresponding general vasodilatory effects of an anaesthetic agent could lead to decreased trans-stenotic driving pressure (and flow) while at the same time increasing flow (decreasing local vascular tone) to other regions of the heart that are already adequately perfused. This could result in a suboptimal redistribution of flow when coronary perfusion pressure is decreased, or when myocardial oxygen demand is generally increased, though this generally does not result in a clinical problem as long as coronary perfusion pressure is re-established [17].

Myocardial protection, or preconditioning, with potent inhaled anaesthetics is a well recognized phenomenon, where the effect of current or recent potent inhaled anaesthetic administration can limit the amount of injury that occurs when the heart is further exposed to ischaemia and infarction. This has been studied extensively in parallel with the heart’s own endogenous protective mechanism of ischaemic preconditioning, which is the most potent form of myocardial protection so far recognized. Myocardial protection by anaesthetic agents may occur through one or more mechanisms. When ischaemia occurs, the anaesthetics can confer beneficial effects through decreasing myocardial work during the ischaemic phase. Much evidence has been presented recently regarding the effects of anaesthetic agents on different aspects of reperfusion and the capacity to reduce the extent of cell death in an area at risk [18,19].

Signalling pathways are to some extent interrupted, and cellular mechanisms which contribute to cell death are mitigated. Laboratory-experimental evidence has supported several possible anaesthetic pre-conditioning effects which lead to reduced amount of cell injury and death when myocardial infarction occurs. These mechanisms include ATPK channels in the sarcolemma and mitochondrial membranes, protein kinase activation and in particular protein kinase C (PKC), as well as signalling pathways associated with reactive oxygen species. These ischaemia-reperfusion cascades lead to either rapid cell death (mitochondrial transition pore activation and cell death) or cell death through apoptosis.

These preconditioning effects are thought to occur in both an early phase, up to several hours, and in a late or delayed phase, which can be at more than one day and possibly longer. Early protective effects (limitation of necrosis or apoptosis initiation) probably have different mechanism compared to late effects, where modulation of inflammation is particularly prominent. Clinical anaesthetic studies have demonstrated protective effects of inhalational agents in terms of less release of injury markers and better post-ischaemia mechanical function [20].
Anaesthetic post-conditioning, or anaesthetics first applied after ischaemia, when the myocardium perfused, can also afford protection to myocardium, and the mechanisms for this effect are currently being investigated. Remote preconditioning, or the application of a stimulus (often an ischaemic stimulus, for example to a limb) has been shown to confer protective effects to myocardium that is later exposed to an ischaemic insult. The mechanisms of protection are not yet clear, though both humoral factors and activation of neural pathways seem to be involved. Though this is not a drug or drug effect, and while there is not yet enough evidence for widespread clinical application, at some point remote preconditioning may become part of the overall anaesthetic management of a patient where an ischaemic cardiovascular (or other) event is expected to occur.

**Key learning points**

- Ultra short-acting hypnotic agents (thiopental, methohexital, propofol) have dose-dependent effects on the circulation, decreasing blood pressure through reduction in vascular smooth muscle tone and cardiac performance, mostly through impairing autonomic nervous system reflexes.
- Ketamine is unique among hypnotics in that it can have some sympathomimetic effects, and does not depress autonomic reflexes when used as a sole agent.
- Dexmetetomidine, a strongly selective alpha-2 agonist which causes hypnosis or sedation as well as analgesia, predictably decreases blood pressure, heart rate, and cardiac output, though if administered too fast can cause hypertension.
- Potent inhalational anaesthetics cause a dose-dependent reduction in ventricular and atrial contractility and diastolic function and depression of baroreceptor reflexes, reducing, so some degree, the compensatory responses to low blood pressure.
- Potent inhalational anaesthetics afford protection for cardiomyocytes that are subsequently exposed to ischaemia. Some protection is conferred even when if the inhalational anaesthetic agent is delivered during or after myocardial ischaemia has occurred.
References