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General Anaesthetic Agents and Their Implication on the Cardiovascular System: A Systematic Review

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Abstract

Background: This review evaluates the possible cardiac side effects of general anesthetic agents upon usage. Cardiac as well as non-cardiac surgery may precipitate adverse events including ischaemia, diverse arrhythmias and reperfusion injury. Volatile and non-volatile anesthetic agents possess cardiovascular effects that can lead to depression of cardiac contractility, arterial pressure, ventricular resistance and reflex tachycardia. However, as not all studies have demonstrated improved outcomes, the risk for undesirable haemodynamic effects must be weighed against the possible benefits of using anaesthetic agents either pre-operatively, intra-operatively or post-operatively during both cardiac and non-cardiac surgeries as well as in patients with coronary artery disease. The halogenated agents all have similar circulatory effects as seen in young, healthy volunteers during maintenance anesthesia (Cahalan MK *et al.*, 1991; Eis S & Kramer J, 2022). The effects of anesthetics on the cardiovascular system have a complicated character, and almost all the anesthetic agents have a dose-related myocardial depression and decreases in heart rate and arterial pressure. During anesthesia, individual responses of patients against procedures such as induction, intubation, and surgical stimulation are influenced by many factors, including preoperatively used drugs, anesthesia type, preferred anesthetic agents, and the autonomic nervous system (Fee JPH *et al.*, 1997, Pagel PS *et al.*, 1991; Smith G *et al.*, 2022).

Keywords: Cardiac, haemodynamic instability, arrhythmias, ischaemia, anaesthetic agents.

INTRODUCTION

In the past decades, both multiple studies and clinical practice have demonstrated the cardiovascular effects of anesthetic agents. These include the early agents of diethyl ether and nitrous oxide to the latest halogenated agents such as isoflurane, desflurane, and sevoflurane.

Anesthesia and surgery have a wide reaching effect on the cardiovascular system. Even in healthy patients having minor operations, anesthetic agents can cause significant cardiac depression and hemodynamic instability. In the patient with pre-existing cardiac disease, these cardiovascular anesthetic effects become much more pronounced, and can lead to serious morbidity and mortality. Patients with cardiac disease may not tolerate wide alterations of hemodynamic variables, and the cardio depressant effects of anesthetics are more pronounced in them. Surgery itself provides many insults and also influences the cardiovascular system, and these may be additive with the effects of anesthesia. It is therefore imperative to select appropriately and adequately the anesthetics that is used for each patient to minimize cardiac toxicity.

General anesthesia is defined as complete anesthesia, affecting the entire body with loss of consciousness, analgesia, amnesia, and muscle relaxation (Brown E.N *et al.*, 2011; Goldman L.S *et al.*, 2011; Siddiqui BA & Kim PY, 2022). There is a wide spectrum of agents able to partially or completely induce general anesthesia. Although the cellular and molecular mechanisms of some of these agents, such as opioids, are well defined, the mechanisms of other anesthetics, such as inhaled agents, are not. Presently, there is not a single universally accepted technique for anesthetic management during surgery. Instead, the drugs and combinations of drugs used are based upon

the pathophysiological state of the patient, individual preference, and experience of the anesthesiologist.

LITERATURE SEARCH STRATEGY

The literature search for this review focused on general anaesthetic agents both volatile and non-volatile. The following search keywords were used for each anaesthetic volatile anaesthetic and cardiovascular complications, non- volatile anaesthetic and cardiovascular complications, cardiac injury, cardiac ischaemia, reperfusion injury, cardiac output and stroke volume, cardiac arrhythmias, E.C.G changes, blood volume and venous haematocrit.

Articles that are not available in English were excluded from the references. The available literature is discussed as related to each area of cardiac toxicity either preoperatively, intraoperatively or post-operatively using anaesthetic agents.

Mode of Administration of Anaesthetic Agents

General anesthetics can either be gases or vapours (inhalational anesthetics), or as injections (intravenous anesthetics or even intramuscular). All of these agents share the property of being quite hydrophobic (i.e., as liquids, they are not freely miscible in water, and as gases they dissolve in oils better than in water) (*Goodman, L. S et al., 2011; Dale, M., 2007).* It is possible to deliver anesthesia solely by inhalation or injection, but most commonly the two forms are combined with an injection given to induce anesthesia and a gas used to maintain it (*Dale, M. 2007).*

Anesthetic gases (nitrous oxide, halothane, isoflurane, desflurane, sevoflurane), also known as inhaled anesthetics, are administered as primary therapy for preoperative sedation and adjunctive anesthesia maintenance to intravenous (IV) anesthetic agents (i.e., midazolam, propofol) in the perioperative setting (Scheiermann P *et al.,* 2018). Inhaled anesthetics enjoy regular use in the clinical setting due to chemical properties that allow the rapid introduction of an agent into arterial blood via the pulmonary circulation compared to the more circuitous route of venous circulation. (Jerath A, *et al.,* 2016).

The most commonly used anesthetic gases are halothane, nitrous oxide, isoflurane, sevoflurane, and desflurane. All inhalational anesthetics provide amnesia and immobility, except for Nitrous oxide, which also provides analgesia. Inhaled anesthetics are commonly used in combination with IV anesthetic agents.

Aside from the clinically advantageous effects of general anesthetics, there are a number of other physiological consequences mediated by this class of drug. Notably, a reduction in blood pressure can be facilitated by a variety of mechanisms, including reduced cardiac contractility and dilation of the vasculature. This drop in blood pressure may activate a reflexive increase in heart rate, due to a baroreceptor-mediated feedback mechanism. Some anesthetics, however, disrupt this reflex (*Goodman, L. S et al., 2011; Katzung, B. G et al., 2014).*

Patients under general anesthesia are at greater risk of developing hypothermia, as the aforementioned vasodilation increases the heat lost via peripheral blood flow. By and large, these drugs reduce the internal body temperature threshold at which autonomic thermoregulatory mechanisms are triggered in response to cold. On the other hand, the threshold at which thermoregulatory mechanisms are triggered in response to heat is typically increased (*Bindra, A, 2017).*

Physiological Effects of Anesthetic Agents on the Cardiovascular System

In William Harvey's great work, *De motu cordis* (1628), it was shown how he was led to his conclusions about the circulation of the blood by exact observations, exact experiments, and exact thought (Harvey, W *et al.*, 1628). Over 300 years since his time there has been new techniques and new devices for the 'investigation of the circulation, and heart function (Michael, J., 1958; Guyton, A.C. 1959). However, there is still no substitute for the three great components of Harvey's method if the anesthetist wishes to determine how anesthetics affect the heart, for there are no clear picture of the many factors involved in normal heart function and how these are affected by stress, disease, and anesthesia (Johnson, S. R,.1951; Siddiqui BA & Kim PY, 2022).

The key role of the heart is that of a unidirectional pump. This pump supplies venous blood to the lungs and arterial blood to the systemic channels which perfuse the vital organs. The brain receives 750 ml/min, which activates nervous functions. The kidney receives 1500 ml/min, which regulates disposal of waste. The liver receives 1500 ml/min, which regulates many of the chemical reactions in the body. The heart muscle itself requires 200 ml/min. These four vital organs normally receive 80 percent of the total blood flow (Prime, F. J. *et al.*, 1952; Pittman RN, 2011).

Another important concept in anaesthesia is the ratio of arterial to venous resistance. This ratio may affect the perfusion pressure in the brain, heart, liver, and kidney, especially during deep anaesthesia, hypothermia, or induced hypotension with ganglion-blocking drugs. When the arterial resistance is increased, the arterial pressure rises without significant change in the cardiac output, whereas increasing the venous resistance causes both the arterial pressure and the cardiac output to fall drastically (Michael, J., 1958; Guyton, A.C. 1959; Delong C, Sharma S. *et al.,* 2022). On the other hand, a proportionate increase in both the arterial and the venous resistance does not lower the blood pressure, but the cardiac output is depressed moderately.

When the blood vessel walls are normal, pre-arteriolar resistance is responsible for 5-15 per cent of aortic pressure. During haemorrhage and deep anaesthesia, pre-arteriolar resistance rises and may be responsible for 50 per cent of the aortic pressure. Under these circumstances, the heart uses up half its energy in getting blood to the arterioles. Tissue perfusion is then reduced considerably.

Cardiac Side Effects of Anaesthetic Agents and Clinical Significance

It is difficult to state the relative safety of any anaesthetic agent with respect to its action on the heart, because this safety depends more on the skill with which each drug is administered, and on the therapeutic measures that the wise anaesthetist employs, than on the inherent properties of any anaesthetic drug (Johnson, S. R, 1951; Pittman RN, 2011).

The cardiovascular effect of each agent depends mainly on the route, rate, and concentration of its administration; on whether the patient is allowed to breathe spontaneously or by augmented ventilation; on the depth and duration of anaesthesia, and on the patient's general physical condition with primary consideration to his pre-anaesthetic cardiopulmonary function and circulating blood volume (Michael, J., 1958; Guyton, A.C. 1959; Eis S & Kramer J, 2022).

The effect of anaesthetic agents on haemodynamics is especially difficult to define because the normal circulation always initiates circulatory reflexes and carries endogenous substances secreted in response to the injected agent. These act on various aspects of circulatory dynamics to prevent over-all change. It is essential, therefore, to record simultaneously as large a number of dependent variables as possible. These variables give a more reliable clue to the major parameters affected and the direction of such change. It is rarely possible to draw conclusions about the mechanisms of circulatory effects of any drug from the changes it may cause in a single dependent variable such as the cardiac output. From the hemodynamic point of view, the most important observations that we should make are continuous or intermittent recordings of:

- Arterial blood pressure,
- Venous blood pressure,
- Heart rate and circulation time,
- ECG,
- Response to posturing,
- Blood volume (plasma and cells) and venous hematocrit,
- Arterial oxygen saturation, pH, pCO2, and oxygen consumption,
- Cardiac output and stroke volume,
- Force of myocardial contraction.

Direct measurement of the arterial blood pressure provides the most important single measurement because: (a) right ventricular output is ultimately reflected in left ventricular output and the arterial blood pressure thus indicating venous return; (b) over-all circulatory effects are evident promptly: (c) instantaneous beat to beat responses can be followed.

There are a few recognized specific effects which each agent exerts on the heart either directly on its force of contraction and on its excitability, or indirectly through release of endogenous hormones, epinephrine, norepinephrine, acetylcholine, histamine or serotonin; or by changing peripheral venous tone, which affects the return of blood to the heart; or through respiratory depression, which causes myocardial hypoxia and acidosis (Prime, F. J. *et al.*, 1952; Suarez- Roca H, *et al.*, 2022).

In general, the depression of respiration by any anaesthetic initially causes an increase in the force of myocardial contraction followed by a progressive decrease. A progressive decrease in myocardial contractility accompanies increasing depth of surgical anaesthesia, regardless of the drug selected. The state of vasoconstriction that is seen before induction of anaesthesia rapidly disappears and peripheral blood flow increases with deepening anaesthesia. This is accompanied by decreased blood flow to the major organs in the body. In the presence of heart disease, all cardiovascular changes caused by anaesthesia are aggravated.

Spinal Anaesthesia

The effect of spinal anaesthesia on the heart is mainly secondary to changes in peripheral arterial and venous resistance, and in blood flow. In general, the effect varies with the height of the sympathetic block, which paralyses the sympathetic vasoconstrictor fibres at the pre-ganglionic level. The specific changes will be outlined with respect to the effects as seen without a vasopressor (Co Tui, *et al.*, 1936; Forman SA & Chin VA, 2008). Sympathetic block at the pre- ganglionic level affects vasomotor tone of the arterioles, which accounts for 60 per cent of the systemic peripherial vascular resistance. The other 40 per cent is maintained by capillary and venous blood flow.

A fall in arterial blood pressure is the most frequent immediate effect of spinal anaesthesia, this is due to denervation of adrenal glands; reduced tone of skeletal muscles, venous dilatation, and pooling of blood; direct paralysis of vasomotor and respiratory centres, as well as hypotension secondary to respiratory insufficiency.

The hypotension following spinal anaesthesia is mainly the result of paralysis of pre-ganglionic sympathetic fibres which transmit motor impulses to the smooth muscle of the peripheral vessels. The degree of

fall in blood pressure is in direct proportion to the number of sympathetic fibres bIocked. Spinal anesthesia given after total sympathectomy produces no change in blood pressure (Pugh, L. G. C.. *et al.,* 1950; Olawin AM & M Das J, 2022).

In some circumstances hypotension: may be predominantly due to a decrease in cardiac output; in others it is primarily due to decreased peripheral resistance, or a combination of both. When both fall during spinal anaesthesia, the loss of peripheral resistance precedes the fall in cardiac output. If the posture of the patient augments venous return and cardiac output is maintained, hypotension is related mainly to the fall in peripheral resistance (Lynn, R. B. *et al.,* 1952; Patel, Kieran *et al.,* 2016).

The relation between the height of the sympathetic block and the degree of hypotension is no more precise than the relation between the height of anaesthesia and the degree of bradycardia. Pulse rate and blood pressure changes vary widely in clinical practice even with the same sensory level of spinal anaesthesia. Pulse rate changes appear to be most closely related to arterial blood pressure alterations, and these are probably related mainly to the changes in venous return to the right side of the heart. Lowering the pressure in the great veins and the right auricle reflexly produces bradycardia (Bainbridge reflex). This may explain the bradycardia that often accompanies even low levels of spinal anaesthesia.

Cardiac output falls almost invariably with high spinal anaesthesia, but the extent of the fall varies widely among patients. There is a general relation between the height of spinal anaesthesia and the fall in cardiac output, which follows the change in venous return to the heart. The depression of venous return is determined by the extent of the sympathetic paralysis, peripheral vasodilatation, and the posture of the patient. During high blocks, most of the pre- ganglionic sympathetic fibres are paralyzed, causing generalized vasodilatation, loss of arteriolar and venous tone, and pooling of a large portion of the total blood volume in the periphery. The extent to which the cardiac output will fall depends on the position of the denervated area with respect to the heart. By having the patient in slight head-down position during high spinal anaesthesia, the decrease in venous return to the heart and in cardiac output is reduced. Head up tilt, on the other hand, may so diminish the venous return and cardiac output that the heart will stop (Lynn, R. B. *et al.,* 1952; Hofhuizen C *et al.,* 2019).

Diminution of stroke volume, particularly when accompanied by bradycardia, is a manifestation of decreased ventricular filling during diastole as a result of the fall in venous return to the heart. Therefore, the extent to which ventricular stroke volume is diminished during spinal anaesthesia is related to the height of the sympathetic block and the position of the patient. The reduction in left ventricular stroke volume which accompanies high spinal anesthesia and which is usually associated with low systemic arterial pressure is quantitatively less than that which occurs when an equal degree of hypotension follows blood loss and peripheral vasoconstriction (Sancetta, S. M., *et al.,* 1952; Bruss ZS & Raja A, 2022).

The power of the heart (myocardial power and ventricular force) is decreased during spinal anaesthesia. This reduction varies directly with the height of anaesthesia, and is caused by the reduction in peripheral resistance the pressure against which the ventricle must force blood during systole and a decrease in stroke volume.

The force of contraction of the myocardium (inotropic effect) is affected by spinal anaesthesia in three ways: decreased ventricular filling according to Starling's Law, reduced end-diastolic blood volume, decrease force of myocardial contraction. Sympathetic paralysis, involving fibres to the adrenal glands, may lower the catecholamine blood level which is the potent endogenous positive inotropic substance and contributes to the force of myocardial contraction; and paralysis of the sympathetic cardiac accelerator nerves, which reduces further the force of contraction (Bennett, L. L. *et al.,* 1948; Bruss ZS & Raja A, 2022).

Although the rate and volume of blood flow through the coronary arteries depend mainly upon mean aortic pressure and secondarily upon myocardial oxygen requirements, coronary flow probably also has self-regulating mechanisms which dilate or constrict the vessels in order to provide the metabolic needs of the myocardium. These changes may be independent of the mean aortic blood pressure.

Spinal anaesthesia may have three circulatory effects: decrease of the total peripheral resistance by interruption of vasoconstrictor impulses to arterioles; pooling of blood in venous circulation, secondary to the post-arteriolar dilatation which reduces venous return to the heart; and decrease in cardiac output due to slowing of the heart rate (Greene, N.M. 1958; Hofhuizen C, 2019).

Diethyl Ether

In spite of the many undesirable effects of diethyl ether, this agent is still the most widely used in clinical anaesthesia. As a primary agent its effect on the heart becomes an important consideration only in the elderly, the debilitated, and those with metabolic disturbances of all the potent general anaesthetic agents, it causes the least respiratory depression for a corresponding level of hypnosis, analgesia, and muscular relaxation; herein lies its safety (Gordh, T.,

1945; Siddiqui BA & Kim PY, 2022). Pulse rate usually increases slightly owing to paresis of the vagal inhibitory mechanism, augmentation of cardio-sympathetic impulses, and liberation of norepinephrine and epinephrine.

Arterial blood pressure rises slightly**.** There is also a widening of the pulse pressure during light planes of anaesthesia, probably for the same reason that the pulse rate rises. However, with increasing depth of anaesthesia, or with prolonged anaesthesia, the blood pressure fall gradually until respiratory depression becomes marked, and then the fall becomes steep.

Cardiac output rises initially in response to the positive inotropic effect of released epinephrine and norepinephrine. As anaesthesia is prolonged, this sympathetic response is exhausted and the depressant effect of Ether on the heart becomes dominant (Bennett, L. L. *et al.*, 1948; Motiejunaite J. *et al.*, 2020). Cardiac output and cardiac power then diminish independently of the depth of anaesthesia. During deep Ether anaesthesia there is also a progressive rise in central venous pressure, which probably indicates increasing depression of myocardial tone that results in a reduction in the stroke volume. Peripheral resistance falls progressively with increasing depth of anaesthesia.

Most laboratory data indicate that Ether is a myocardial depressant, but in man the sympathetic stimulation or liberation of catecholamines produces a positive inotropic effect on the heart that overcomes the depressant influence of Ether on the myocardium if the patient is healthy (Fletcher, G. *et al.*, 1956; Schömig A, 1990).

Cyclopropane

The main difference between Ether and Cyclopropane is that Ether causes severe respiratory depression during surgical anaesthesia. When adequate artificial respiration is provided, the cyclopropane content of the blood can be increased to a level of about 20 percent above that necessary to produce respiratory arrest without affecting the human heart. At higher concentrations, cyclopropane has a direct myocardial effect which causes serious arrhythmias and heart failure (Drips, R.D., 1947; Schömig A, 1990).

The effects of Cyclopropane on haemodynamics are complicated because it has both sympathomimetic and parasympathomimetic properties. A direct sympathomimetic effect or response to release of norepinephrine appears evident from increases in pulmonary artery pressure, central venous pressure; and total peripheral resistance. The slowing of the heart rate may be a parasympathetic response, which is increased by morphine premeditation (Price, H. L., *et al.*, 1953).

Cyclopropane has less effect on the peripherial circulation than have the other potent agents. For this reason it is considered by most anaesthetists to be the best agent to use on patients in compensated or frank shock particularly that due to acute blood loss and intestinal obstruction (Buckley, J. J, *et al.*, 1953; Miller A.L. *et al.*, 2022).

Hypotension often occurs at the end of Cyclopropane anaesthesia, especially when pulmonary ventilation has been inadequate. The post-anaesthetic hypotension after Cyclopropane is often difficult to correct.

During surgical planes of Cyclopropane anaesthesia there is a moderate fall in cardiac output, but peripheral vascular tone remains within normal limits or may be elevated; and the central venous pressure may be elevated. The latter is more likely a sign of increased blood flow from the periphery than a sign of myocardial incompetence since patients fare better with Cyclopropane during shock and haemorrhage than with the other potent agents (LI, T. H., *et al.*, 1957; Miller A.L. *et al.*, 2022).

Trichlorethylene

This agent is very toxic to the heart when used as a total anaesthetic in comparison with Cyclopropane. It should never be used for major procedures without sufficient supplementation to reduce the concentration required below 1 per cent. When used in a balanced anaesthetic technique with Nitrous oxide and oxygen (3:1 or 2:1), it provides excellent analgesia and hypnosis, and a very smooth anaesthetic course with less than 0.5 per cent (Hewer, C. L., *et al.*, 1941; Erhardt W *et al.*, 1988).

In clinical use with supplements, it has little effect on blood pressure or pulse rate, causes moderate peripheral vasodilatation, however, even in 1 per cent concentration sensitizes the myocardium to epinephrine. Spontaneous arrhythmias are rarely seen when the concentration is less than 1 per cent, particularly when pulmonary ventilation is augmented (Waters, R. M., *et al.*, 1943; Erhardt W *et al.*, 1988). Arrhythmias become common when the concentration exceeds 1.5 per cent, and are seen more than with any other agent if 2 per cent is exceeded, especially if breathing is spontaneous and tachypnoea is allowed to persist (Barnes, C. G., *et al.*, 1944). Ventricular fibrillation with epinephrine is highly likely during anaesthesia with trichlorethylene. For prolonged anaesthesia 0.5 percent should NOT be exceeded (Ostlere, G. 1953; Reuter S *et al.*, 2014).

Chloroform

The effect of chloroform on the heart is important because cardiac death may occur quickly if it is not administered carefully. It may stop the heart in three ways: by direct myocardial depression, by ventricular fibrillation, and by vagal inhibition. When this agent is used for major procedures, an accurately

calibrated vaporizer should be employed to control its rate of administration (Levy, A. G. 1914; Polania Gutierrez JJ *et al.*, 2022).

Blood pressure falls gradually as depth of anaesthesia is increased owing to reduction in peripheral resistance (vasomotor centre depression), myocardial tone and force. The systolic pressure falls more than the diastolic pressure, causing a small pulse pressure when more than 1 per cent is administered. Pulse rate falls gradually as depth of anaesthesia increases. This slowing of the pulse is a vagal reflex, because atropine prevents or reverts it (Waters, R. W. 1951; Siddiqui BA & Kim PY, 2022). With prolonged anesthesia, the slowing of the pulse may no longer be vagal, but rather may be due to a direct effect of chloroform on the heart, or to the indirect effect from a failing circulation (Armstrong D, M. H., 1959; Siddiqui BA & Kim PY, 2022). Cardiac output falls with excessive chloroform anaesthesia owing to the depression of myocardial tone and ventricular force (Armstrong D, M. H., 1959; Akata T, 2007).

Under light anaesthesia with Chloroform, some patients develop minor cardiac arrhythmias owing to the vagal effect on the heart. The heart is also sensitized to catecholamines, which will cause ventricular fibrillation especially if pulmonary ventilation is not adequate. The anesthetic use of chloroform has been discontinued because it caused deaths due to respiratory failure and cardiac arrhythmias.

Fluothane

Fluothane has a characteristic action on the heart and circulation that lies closer to Chloroform than to Cyclopropane when used in the concentration required for surgical anaesthesia (0.5 to 1.0 per cent). It is slightly more potent than Chloroform in producing cardiovascular depression, but it is less potent as hypnotic (Johnstone, M. 1956; Miller A.L. *et al.*, 2022).

Blood pressure depression is related to the rate and concentration used. When administered slowly from an accurately controlled vaporizer in less than 1 per cent concentration, severe hypotension can usually be avoided (Severinghaus, J. W., 1958; Rubio-Guerra AF *et al.*, 2013). During maintenance of anaesthesia, the blood pressure usually rises somewhat above the induction level, but remains below the control level. Hypotension is more likely to occur with muscle relaxants such as d'tubocurarine than with Gallamine or Succinylcholine. Pulse rate is usually lowered, but marked bradycardia is not common, and can often be eliminated by full atropinization. As with cyclopropane, there may be a pulse deficit due to ectopic heart beats (Dobkin, A.B. 1958; Arnold RW, 2021).

Peripheral blood flow is increased markedly, while peripheral resistance is only slightly reduced. Ventricular force is reduced as the depth of anaesthesia is increased. The slight reduction in peripheral resistance and marked reduction in myocardial power result in a fall in cardiac output (Dobkin, A.B. 1958; Arnold RW, 2021).

Fluothane anaesthesia has a predominant vagal effect on the heart. This moves the pacemaker from the sino- auricular node to the atrioventricular node when excessive depth of anaesthesia or inadequate ventilation is permitted. Depression of the sino-auricular node results in discharges from ectopic centres and a nodal rhythm appears (Wyant, G. M., *et al.*, 1958; Kashou AH, 2022). Arrhythmias may occur during rapid reduction and during deep anesthesia, but usually disappear if the concentration of Fluothane is reduced, ventilation is improved, and atropine is administered.

Intravenous Barbiturates

The pre-anaesthetic state of the myocardium and peripheral circulation is an important factor in the clinical response to intravenous barbiturates (thiopental, thiamylal, hexobarbital, methitural, buthalitone, methohexital) (Etsten, B., *et al.*, 1955; Syed Q, 2022). They have a potentially powerful depressant effect on the myocardium, as indicated by experiments on the heart-lung preparation. However, when given with care, and supplemented by nitrous oxide-oxygen and muscle relaxants, they are no more depressing to the cardiovascular system than ether or cyclopropane (Daniel, E. E. *et al.*, 1956; Miller AL, 2022).

Rapid injection of a large dose of barbiturates may cause a profound fall in arterial pressure. This is due mainly to peripheral vasodilation, loss of peripheral venous tone, reduction of venous return to the heart, pooling of blood in relaxed peripheral veins, and fall in cardiac output. These may be due to a direct toxic effect on the myocardium which impairs contractility of the heart. The patient with an impaired myocardium has a greater fall in blood pressure than does a fit person. Any pre-existing coronary insufficiency is increased by the myocardial hypoxia following hypotension, and further decreases the efficiency of the heart muscle (Daniel, E. E. *et al.*, 1956; Boyette LC & Manna B, 2022).

Patients with hypertension are more likely to have a marked fall in blood pressure. Peripheral vasoconstriction on account of haemorrhage is also lost very quickly with barbiturates, causing profound hypotension. When peripheral vascular tone is already reduced by ganglionic blocking drugs or other vasodilator drugs, the hypotensive effect of barbiturates is exaggerated. Severe hypotension is more likely in elderly patients if the upright posture is adopted. Patients who are "vagotonic" or have a labile blood pressure are also more likely to have a sharp fall in blood pressure with barbiturates (Dobkin, A. B., *et al.*, 1957; Yaghoobi S *et al.*, 2015). Barbiturates are rarely the primary cause of cardiac arrhythmias. Occasionally,

ventricular arrhythmias are reported. These may occur if ventilation is inadequate, and the heart becomes hypoxic (Dobkin, A. B., *et al.,* 1957; Bhutta BS, *et al.,* 2022).

Procaine, Lidocaine, and Related Esters

When administered intravenously, procaine, lidocaine, and their related esters have an action on the heart which is similar to that of quinidine (Graubard, D. J., 1950; Sheikh NK *et al.,* 2022). They are protoplasmic poisons which manifest their action on the heart by depressing the conductivity in the ventricles as well as the atrioventricular node and the auricles (Steinhaus, J. E., 1957; Makarovsky I *et al.,* 2008). They prolong the refractory period and decrease the excitability of the sino-auricular node and the myocardium, thereby slowing the heart rate. The slowing is not accompanied by an improved capacity of the heart to contract, as is seen with digitalis, but renders the heart less excitable to stimuli and retards the rate of conduction of normal impulses. Large doses also reduce the contractility of the heart, and may cause severe hypotension. Lidocaine causes less vasomotor depression than procaine when used as an intravenous supplement to general anaesthesia (Kimmey, J. R., *et al.,* 1959; Beechan GB *et al*., 2022). Procaine prolongs the PR interval and QRS complex. Excessive doses may cause premature beats, tachycardia, and ventricular fibrillation.

Halogenated Anaesthetic Agents

Halogenated agents, including sevoflurane, desflurane, isoflurane, enflurane, and halothane, all decrease mean arterial pressure (MAP) with increasing concentrations of the anesthetic gas in a dose-dependent manner (Brioni JD *et al.,* 2017; Torri G 2010; Tanaka S, 1996). The mechanism of the decrease in MAP is related to a decrease in systemic vascular resistance (SVR) except halothane, which decreases the MAP by directly affecting the myocardium and thereby decreasing cardiac output (CO) without changes in SVR. (Torri G 2010; Tanaka S, 1996) Sevoflurane has demonstrated to have less of an impact on hemodynamic and cardiovascular parameters than desflurane and isoflurane, caleading to reduced morbidity and mortality (Brioni JD *et al.,* 2017;Li F, Yuan Y. 2015). Nitrous oxide, different from other inhaled anesthetics, does not affect mean arterial pressure. Thus, when nitrous oxide is combined with halogenated agents, the reduction in MAP is minimized or even reversed (Becker DE *et al.,* 2008; Weiskopf RB *et al.,* 1991).

Cardiac output (CO) is reduced with increasing concentrations of inhaled anesthetics (Brioni JD *et al.,* 2017; Cahalan MK *et al.,* 1991). In healthy individuals, this reduction in CO is partially compensated by an increase in heart rate. Therefore, at clinically relevant concentrations and in healthy adults, the cardiac output is usually preserved. Comorbidities, older age, and concurrent medication may inhibit this compensatory mechanism, resulting in an overall reduction of CO (Das S *et al.,* 2010).

Tachycardia is commonly seen during maintenance administration of halogenated inhalation agents and is thought to be compensatory to the reduction in cardiac output as described above. The heart rate is dose-dependent as concentration increases, and is slightly different for each agent. The concentration of inhalation anesthetics is standardized by the minimum alveolar concentration (MAC), a known concentration of inhaled anesthetic at which fifty percent of patients do not elicit a physical response to a painful stimulus. The different responses between agents may be related to the balance between sympathetic and parasympathetic activity. Isoflurane is seen to only increase sympathetic activity, whereas sevoflurane increases both sympathetic and parasympathetic activity as seen when combined with nitrous oxide. (Nishiyama T, 2016).

Other Factors Associated with Anaesthesia that Affect the Heart

Hypoxia

Mild hypoxia of short duration causes an increase in the heart force owing to reflexes mediated through the carotid body and sympathetic effectors in the spinal cord. When the carotid body or spinal cord (up to C2) is blocked, the effects of hypoxia on the heart are very much augmented, causing a sharp fall in the force of myocardial contraction, and if the hypoxic condition persists, cardiac arrest follows quickly (Woods, E. F., *et al.,* 1959; Schultz HD, *et al.,* 2013).

Acidosis

The effects of metabolic and respiratory acidosis are not usually evident during anesthesia, but they may be a direct effect of hypoxia. The cardiac output decreases as hypercarbia develops, but the output may be restored to normal with the catecholamines. The depressant effect of acidosis on the heart is due mainly to the fall in pH back to 7.40 in the presence of hypercarbia which tends to restore the myocardial force and contractility (Miller, F. A., *et al.,* 1952; Schultz HD, *et al.,* 2013).

Heart Disease

The maximum work that can be performed by the heart at any given filling pressure is decreased substantially by the stress of body trauma, hypoxia, acidosis, and especially by disease of the myocardium (Hopkins, A. L., *et al.,* 1955; Boyette LC & Manna B, 2022).

Induced Hypotension

The main result of induced hypotension is the creation of a disparity between the circulating blood volume and the capacity of the vascular bed. The effect on the heart of such a change depends more upon the

physical condition of the patient, the areas which are rendered ischaemic and the duration of ischaemia; than on the absolute blood pressure at heart level, regardless of the method used to lower the blood pressure (arteriotomy, total spinal block, postural, ganglion blocking drugs, etc.) In general, a blood pressure that is less than 80mmHg at heart level is critical to the adequate perfusion of the vital organs, and should not exceed a time limit that is related especially to the known recovery time for normal function of the brain, heart, spinal cord, kidney, and liver (Nahas, G.G., 1959; Song Q, *et al.*, 2022).

Airway Pressure

The circulatory effect of positive pressure in the airway has been known for almost a century (Quincke, H., *et al.*, 1871; Potchileev I *et al.*, 2022). Detailed studies have been carried out in recent years, and all have shown that whenever air, anaesthetic gases, or vapors are forced into the lungs, there is interference with the circulation if the mean airway pressure is permitted to rise (Belcher, H. K., *et al.*, 1943; Tobias JD, 2010). This interference is especially marked when the patient has a reduced circulating blood volume (Werko, L., 1947; Thompson, S.A., 1948; Sharma R, Sharma S., 2022). The least disturbance of circulation during artificial respiration is achieved when the positive pressure phase is less than one-third of the breathing cycle. During the expiration phase of the breathing cycle, the airway pressure must drop to zero or sub-atmospheric pressure to compensate for the circulatory impedance which occurred during inspiration (Cournand, A., *et al.*, 1948; Hubay, C. A. *et al.*, 1954; Gold WM & Koth LL. 2016). The degree of circulatory embarrassment occurring with intermittent positive pressure is determined by the magnitude of the mean airway pressure and the duration of the inspiratory phase (Dobkin, A. B. 1958; Morch, E. T., *et al.*, 1959; Potchileev I *et al.*, 2022).

Abnormal Cardiac Rhythms

Abnormal cardiac rhythms may develop during anaesthesia (Kurtz, C. M., *et al.*, 1936; Kwon CH & Kim SH, 2017). They are usually caused by a direct effect of the drug on the heart, which may shorten the refractory period, depress the resting electrical potential, or alter the secretion of endogenous substances (for example, catecholamines) (Meek, W.J. 1941; Milowski, J., *et al.*, 1943; Bauer M, 2017). Hypoxia, hypercarbia; elevated blood potassium, and a variety of external stimuli also cause abnormal cardiac rhythms (Burstein, C. L. 1946; Geovanini GR & Lorenzi-Filho G, 2018). Stimulation or traction of the lung hilus, ribs, stomach, incision of a diseased pleura or pericardium, mechanical pressure on the vagus nerve or carotid sinus, and handling or rotating a diseased heart are particularly likely to cause serious arrhythmias (Joseph, S. I., *et al.*, 1951; Niehues LJ, 2022). In general most spontaneous arrhythmias may be prevented or reverted by reducing the concentration of the primary anaesthetic agent and increasing pulmonary ventilation to eliminate the possibility of hypoxia and hypercarbia (Melville, K. I., 1954; Miller AL, *et al.*, 2022).

Issues of Concern

Sevoflurane, desflurane, and isoflurane all prolong the QT interval on the electrocardiogram in healthy adults without concurrent medication. (Yildirim H *et al.*, 2004). When administering inhaled anesthetics to patients with known congenital or acquired long QT interval syndrome (LQTS), there is some concern for developing malignant arrhythmias. (Booker PD *et al.*, 2003) There have been multiple case reports of patients with congenital LQTS who have developed torsade de pointes after administering inhaled anesthetics (Kumakura M *et al.*, 2016; Choromanski DW *et al.*, 2016). However, when used in conjunction with preoperative beta-blocking agents, patients with known LQTS have been safely anesthetized using all modern inhaled anesthetics (Booker PD *et al.*, 2003; Delgado-Herrera L *et al.*, 2001). Of note, a recent study of pediatric patients aged 2 to 12 undergoing general anesthesia with sevoflurane or desflurane demonstrated no effect on the QT interval regardless of which anesthetic agent was in use (Lee JH *et al.*, 2018).

There is debate regarding the use of inhaled anesthetic agents versus intravenous anesthetic agents during coronary artery bypass surgery in patients with coronary artery disease (Brioni JD *et al.*, 2017). Numerous studies have conflicting results when comparing overall morbidity and mortality outcomes. More recently, multiple large meta- analyses have demonstrated that sevoflurane may exhibit a more favorable cardioprotective effect during cardiac surgery than propofol, although they failed to demonstrate differences in morbidity and mortality (Li F, Yuan Y. 2015; Landoni G *et al.*, 2014). While there were concerns that isoflurane may induce coronary steal syndrome, halogenated agents have instead demonstrated ischemic preconditioning effects on the myocardium in the setting of compromised regional perfusion. Two windows of protection have been demonstrated; the first window appears for the first one to two hours after the conditioning episode and then dissipates. The second window appears twenty-four hours after the conditioning episode and may last as long as three days. (Li F, Yuan Y, 2015) The mechanism of protection in cardiomyocytes has been linked to selective priming of mitochondrial adenosine triphosphate-sensitive potassium channels (mK-ATP channels) through multiple triggering protein kinase C-coupled signaling pathways (Zaugg M *et al.*, 2002; Landoni G *et al.*, 2007). Despite the current amount of evidence, further studies are recommended to assess the clinical significance of perioperative cardiac protection using inhaled anesthetics (Chen S *et al.*, 2018).

All anesthetic gases have shown a depression of cardiac contractility; halothane reduces arterial pressure, and the other volatile gases decrease vascular resistance due to vasodilatation resulting in preserved cardiac output. These effects can cause sympathetic activation and reflex tachycardia, especially with the use of isoflurane and desflurane, which cause less baroreceptor reflex depression than the others. Volatile gases can also sensitize the myocardium to catecholamines, potentially increasing the risk of ventricular dysrhythmias if patients were given sympathomimetic drugs perioperatively. These effects can be balanced with blood pressure regulation using (hydralazine, labetalol, verapamil, etc.) and HR control (metoprolol, amiodarone, etc.). Isoflurane, sevoflurane, desflurane will decrease systemic vascular resistance leading to a drop in systemic blood pressure. These changes are more profound in hypovolemic patients.

Almost all anesthetics have some effects on cardiac electrical activity (Staikou C *et al.*, 2014). Propofol seems to have the least effect (Hume-Smith HV *et al.*, 2008; Scalese MJ *et al.*, 2016). Sevoflurane in different studies could prolong the QTc interval yet it had no effects on Tp-e (Scalese MJ *et al.*, 2016; Whyte SD *et al.*, 2007). The effects of sevoflurane on cardiac electrophysiology in healthy children and adults as well as patients prone to repolarization abnormalities in comparison with normal subjects has been evaluated in different studies (Scalese MJ *et al.*, 2016; Whyte SD *et al.*, 2005; Kuenszberg E *et al.*, 2000, Hanci V *et al.*, 2010).

Unlike propofol, it seems that sevoflurane could increase QT interval. Sevoflurane can block delayed potassium channels and prolong QT and QTc in children and adults (Whyte SD *et al.*, 2005; Han DW *et al.*, 2010).

CONCLUSIONS

This review gives credence to the fact that the choice of an anesthetic regimen has an impact on patients" outcome following cardiac surgery. Anesthetics have cardiac depressant effects that decrease myocardial oxygen demand and may have a beneficial role on myocardial oxygen balance during ischaemia. Evidence exist that volatile anesthetic agents have direct protective properties against ischaemia myocardial damage. A careful consideration of each anesthetic and its attendant effects on the body as a whole is essential to providing care either pre-operatively, intra-operatively or post-operatively for a cardiac or non-cardiac patients to mitigate cardiac toxicities.

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