The effect of Anaesthetic agents on myocardial function

An historical perspective

When I began working in Anaesthetics I came from a background in Cardiology. With this bias in mind I was distracted by just how normal all our patients ECG’s seemed to be. I had definitely acquired a skewed perspective working with dickey tickers all those years.

As the months rolled by the most conspicuous arrhythmias which seemed to make a regular appearance under Anaesthesia were nodal rhythm and sinus bradycardia. I also wondered about the strain and stresses of surgery and anaesthesia on the myocardial oxygen demand and the effects of anaesthesia on ventricular function, preload and afterload. With the multi drug approach used to induce and maintain an anaesthetic I was keen to learn just how do patients hearts cope with this barrage of pharmaceuticals and which ones (I wondered) have caused the most grief for patients and anaesthetists over the years. The more I looked into this subject the more I realised the answers are not straight forward. However, keen to understand more I pressed on with my enquiry. After extensive reading around the subject I came to the realisation that this multifaceted issue was more than could ever be compressed into an essay, well certainly not by me.

What follows is my laypersons impression of some of the issues to consider regarding Anaesthetic pharmacology and the heart.

I am going to start by briefly covering what is normal in regard to heart rhythm and function in the hope that what is abnormal may be more easily recognized.

The normal heart rhythm, sinus rhythm, is the result of an electrical impulse travelling through the heart’s conducting tissue.
The resulting waveform is the electrocardiograph.

In the normal course of events the heart's rhythm originates in the sinus node. Arrhythmias such as nodal rhythm and ventricular tachycardia are the result of an irritable focus elsewhere in the heart taking over the conduction pattern. This is significant as generally the result haemodynamically speaking will be less efficient.
Another aspect to consider with heart function is that of oxygen supply and demand. When the demand of the myocardium for oxygen is greater than that supplied in the coronary arterial circulation the myocardium can become ischaemic. Heart muscle which lacks adequate oxygen supply can be seen as changes on the ECG. Depending on the area of the heart affected different changes can be seen. When the ventricles of the heart become ischaemic this can manifest as changes to the ST segment and t wave of the ECG. Changes which may be seen include t wave flattening or inversion (which was previously upright) and ST segment depression or elevation. Changes of greater than 1 mm in bipolar leads and 2mm in unipolar leads. These changes in themselves are not diagnostic but may prompt an anaesthetist to further investigate with a 12 lead ECG and blood tests.

When the heart muscle supplying the conduction system becomes ischaemic arrhythmias and QRS morphology changes can be seen. For example if the RCA which supplies the sino-atrrial node becomes severely ischaemic sinus rhythm may be compromised and an escape rhythm (such as nodal) may take over.

A patient’s exercise tolerance is often a good indicator of their myocardial health, as also is their drug usage and dosages.
A patient, ideally, should not have an elective surgical procedure within six months of myocardial infarction as there is a higher incidence of re-infarction associated with elective surgery within this period.

The filter setting on the ECG monitor also needs to be taken into consideration. Most modern monitors allow us to change the filter on the ECG signal. When choosing the monitor option the practical implications of our choices need to be considered. E.g.: A five lead cable will give as a greater range of analysis. V5 offers a good diagnostic lead for ST analysis. Is ST analysis relevant for a particular case.

**Electrode placement for precordial leads (for 12-lead ECG option)**

**V1** 4th intercostal space, right of sternum

**V2** 4th intercostal space, left of sternum

**V3** midway between V2 and V4

**V4** 5th intercostal space, in the midclavicular line

**V5** same level as V4, at anterior axillary line (between V4 and V6)

**V6** in 5th intercostal space, in the midaxillary line

A high pass filter of 0.5 – 100 Hz will distort low frequency signals such as the ST segment.
A low pass filter of 0.05 – 40 Hz will eliminate AC interference (of 50 Hz), will distort the high frequency signal of the QRS complex, but is useful for ST segment analysis.
A diagnostic frequency range will include 0.05 – 100 Hz ie: there is no filter.
A notch filter will cut out the frequency around 50 Hz to eliminate AC interference.

Einthoven's Triangle for calculating the mean electrical axis of the heart
Different diagnostic leads give us different information. So depending on which lead we are looking at we may miss relevant info. Limb lead II is in the same mean electrical axis as the heart so is generally a useful lead for monitoring the heart rhythm.
V5 is the definitive diagnostic lead for cardiac axis and left ventricular ischaemia. For these reasons combined it is helpful wherever possible to place your intraoperative ECG leads in the V5 chest position with the remaining leads on the left and right shoulders.

When interpreting an ECG recording it is useful to take note of the baseline recording and trends information. It is also helpful to consider the appearance of the baseline 12 lead ECG.
Left Ventricular function is less easily monitored during anaesthesia. For patients with cardiac symptoms a baseline echocardiogram may be appropriate to establish LV function status. For those patients with a compromised Ejection Fraction (of < 50%) it may be appropriate to assess intraoperative Cardiac Output (using thermodilution & a Swan-Ganz catheter) or a trans-oesophageal echocardiogram intraoperatively.

Cardiac output is the amount of blood ejected by the heart with each beat. The formula for cardiac output is:

**Cardiac Output = Heart Rate X Stroke Volume**

The body is always trying to keep in balance with this formula. For example, if someone had a Myocardial Infarction the stroke volume would decrease because of the weakened heart muscle's inability to pump out enough blood. To keep in balance, the heart rate would have to increase. On the other hand, the person who is athletic has built up the heart muscle so well that the stroke volume increases. As a result, he/she can manage well, with a slow heart rate, to meet the cardiac output.

Many elderly patients are now beta blocked (to decrease the work of the heart). But as long as their blood pressure is adequate, we often accept very slow heart rates e.g. 40 bpm.
Preload is a passive stretching force exerted on the ventricular muscle at the end of diastole. Preload is caused by the volume of blood in the ventricle at the end of diastole. If a patient is overhydrated, preload will increase. If a patient is dehydrated, preload will decrease.

Afterload is the force resisting the contraction of the cardiac muscle fibers. That is the end-systolic wall stress in the ventricle. It is determined by two conditions; the blood volume ejected from the ventricle and the compliance of the vascular space into which the blood is ejected. Think of afterload as a hose nozzle. If the hose nozzle is wide open, afterload is decreased due to decreased compliance. If the hose nozzle is almost closed, afterload will increase because the water has so much resistance to push against. Increased blood pressure is increased afterload, while decreased blood pressure is decreased afterload.
Contractility refers to the ability of cardiac muscle fibers to shorten when stimulated. The heart muscle is much like a rubber band. The more you stretch it, the better it will contract. That is up to a point, like a rubber band the heart muscle will fail if stretched to far. Contractility can be affected by a variety of chemicals, both natural as well as externally acquired.

As heart rate increases, the amount of blood that it can pump during a given time also increases until a critical heart rate is reached then cardiac output decreases. In combination these factors all work together to allow the heart to compensate over a wide range of conditions. This allows for the continuous supply of oxygen and nutrients to all parts of the body.

For the purposes of this discussion I have narrowed my investigation down to include:

- Inhaled anaesthetics – Volatiles and Nitrous oxide
- Intravenous induction agents
- Opioids
Atrial Fibrillation [AF] is a common cardiac arrhythmia. Incidence is 5 – 10% in the over 65 years. AF may be paroxysmal (i.e. intermittent) or sustained. AF is characterized by rapid atrial contraction, >400 beats/min, with minimal mechanical activity. Only a small proportion of atrial impulses are conducted into the ventricles.

*Most anaesthetic agents have a minimal effect on AF.*

Halothane sensitizes the myocardium to catecholamines (e.g. adrenaline), and this may drive atrial fibrillation.

Other volatile agents appear to have a protective effect, with antifibrillatory effects on the myocardium following ischaemia or reperfusion similar to calcium channel blockers.

Isoflurane depresses sinus node automaticity and AV nodal conduction, and has antifibrillatory effects on atrial tissue.

Temporary conversion of AF to normal sinus rhythm, during anaesthesia, has been reported.

*Most anaesthetic agents have minimal effect on AF.*

AF may be induced by some procedures for which anaesthesia is given: ECT, Cardiac & Thoracic surgery.
The commonest cardiovascular complications of anaesthesia are arrhythmias and hypotension.

Hypotension is never far away under General Anaesthesia. Most anaesthetic agents tend to produce some degree of depression of the heart and peripheral vasomotor tone either directly or by their depressant action on the brain.

**Inhaled anaesthetics – Volatiles and Nitrous oxide**

Volatile anaesthetic agents, inhaled into the lungs, will first enter the circulation and are then carried to all tissues of the body. We are primarily interested in the concentration reaching the brain because this produces the state of anaesthesia. The exact mechanism of anaesthesia is poorly understood but it seems that the nerve cells absorb the agent and in so doing their ability to conduct impulses to each other is reduced.

The more soluble the agent is in blood the longer it takes to build up an effective concentration in the brain and the slower the onset of unconsciousness. Thus with a very soluble agent such as ether, the induction of anaesthesia is prolonged. On the other hand an agent such as nitrous oxide is relatively insoluble in blood; the blood becomes saturated quickly, the brain concentration rises quickly and the effect is seen rapidly.

Historical agents have a greater adverse effect than today’s agents.

Data from healthy volunteers breathing equally potent concentrations of halothane, enflurane, isoflurane, desflurane and nitrous oxide have provided the foundation for establishing comparative differences of inhaled anaesthetics on circulation. It must always be appreciated, however, that surgical patients with co-existing factors such as disease, drug therapy or surgical stimulation can respond differently to healthy volunteers. The effect on the circulation is found to be dose-dependent and drug specific.
**Arterial BP**
Generally, all inhalational agents decrease the blood pressure.
- Halothane and enflurane provide a decrease in BP due to decreases in myocardial contractility and cardiac output
- Isoflurane and desflurane decrease blood pressure due to peripheral vasodilation ($\downarrow$SVR)
- N2O (alone) does not alter blood pressure.

**Heart rate**
- HR is unchanged by halothane
- Deep levels of desflurane (mac>1) can increase HR
- Isoflurane can increase HR (most notable in the elderly)
- Enflurane causes a dose dependant increase in heart rate.
- N2O causes only a minimal increase in HR

These changes are thought to be due to stimulation of the carotid sinus baroreceptors. Halothane (which is known to inhibit this reflex) causes no such change to HR despite its hypotensive effect.

**Cardiac Output**
- Halothane and enflurane produce dose-dependent decreases in CO.
- Nitrous oxide causes a mild increase in CO

**Stroke Volume**
- Volatile anaesthetics cause a dose-dependent decrease in stroke volume ($SV = CO/HR$). The resulting CO, however, can remain unchanged due to the increase in HR.
- SV is unchanged by N2O

**Contractility**
Direct myocardial depression was seen invitro, when the effect of inhaled anaesthetic agents on papillary muscle was studied historically. This result, however, had not been observed invivo. Presumably due to the compensatory homeostatic mechanisms. This influence of volatile anaesthetics on contractile function, however, has been studied extensively in recent years. It is now widely agreed that volatile agents do cause dose-dependent depression of contractile function. This effect is more pronounced in halothane and enflurane than it is in isoflurane, desflurane or sevoflurane.

**Rhythm**
- Halothane decreases the amount of circulating adrenaline required to provoke ventricular ectopics. (This effect is less notable in children).
• Nodal rhythm (resulting in ↓BP) is common during inhalation of halothane.
• Volatile anaesthetics lower the arrhythmogenic threshold to catecholamines. Resulting in an increased likelihood of arrhythmias.

**Duration**
• Inhalation of volatile anaesthetics (>5 hrs) is associated with an ↑BP & ↑CO.

**Myocardial Ischemia**
• Volatile anaesthetic agents have been demonstrated to attenuate (gradually decrease) the effects of myocardial ischemia in acute coronary syndrome.
• Halothane and Isoflurane facilitate (improve) the recovery of stunned myocardium.

The common denominator concerning the changes of myocardial function during anaesthesia is the activity of the sympa-ho-adrenal system. Evidently, all anaesthetic agents at equipotent dose levels will depress myocardial function in the isolated heart, showing their direct effect upon the myocardium. However, the depressant effects of anaesthetic drugs are antagonized by the responses of cardio-regulatory mechanisms. Myocardial depression becomes evident when the compensatory mechanisms are blocked.

*Inhalational agents: decease blood pressure  
Decrease cardiac output  
Cause a minimal change to Heart rate  
(Except Isoflurane for which the change in HR is more noticeable)*

Adverse effects of inhalational anaesthetic agents can include:
Decreased myocardial contractility  
Reduced cardiac output  
Hypotension  
Arrhythmias  
Increased myocardial sensitivity to catecholamines  
Dose dependent cardio-respiratory depression

**Isoflurane** increases HR. Decreases BP via systemic arterial dilatation

**Sevoflurane** Decreases BP

**Desflurane** Decreases BP
**Enflurane**  Decreases BP Can decrease CO

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Figure 4-5. Comparison of the cardiovascular effects of volatile anesthetics [halothane (solid red line), isoflurane (solid black line), desflurane (dotted red line)] during mechanical ventilation of the lungs in otherwise healthy volunteers. MAP, mean arterial pressure; HR, heart rate; SVR, systemic vascular resistance; CVP, central venous pressure. (Adapted from Weiskopf et al., with permission.)
CHLOROFORM

Chloroform was first used as an anaesthetic in 1847 by James Simpson. He realised how much more potent chloroform was than ether. By 1848 chloroform had claimed its first victim, a 15 year old girl called Hannah Greener. Investigation into this death occurred but it was only many years later, in 1911 that experiments by Levy and Lewis proved that deaths from Chloroform were: “Not due to the respiratory depression but due to the cardio toxic effects resulting in cardiac fibrillation”.

When animals in this study inhaled chloroform at 0.5% or 2.0% in air and then received a bolus intravenous injection of adrenaline (total dose, up to 65 micrograms [µg]), they had a electrocardiograph pattern, of short pauses in heartbeat followed by tachycardia. Continued administration of chloroform ultimately resulted in ventricular fibrillation. Later studies showed that the variations in cardiac sensitivity depended on the duration and degree of anaesthesia (Levy 1913). Light anaesthesia with chloroform produced more cardio toxic effects than deeper surgical anaesthesia, possibly because of a decrease in central nervous system impulses to the heart. Levy found a number of published cases in which humans had been overcome by chloroform and medical treatment had consisted of injecting adrenaline (to stimulate the cardiovascular system). In many cases, the patients died after exhibiting tachycardia followed by ventricular fibrillation.
Ether, then known as “sweet oil of Vitriol” was discovered by Valerius Cordus in 1540.

Crawford long administered ether in 1842 on a patient having a cyst excised. Long did not publish his results and is hence not credited with discovery of Anaesthesia.

Ether is an agent made from sugar cane (ethanol). It is stored in dark bottles as light may decompose it. If it is taken to high altitude its boiling point is lowered (for example where atmospheric pressure is 425 mmHg ether will boil at 20°C).

Ether has been known since the 16th century as "sweet vitriol" but only when W.T.G.Morton demonstrated its effects in Boston in 1846 did its anaesthetic properties become known worldwide.

**Advantages:** Ether stimulates respiration and blood flow due to its mimicking of the effect of adrenaline release. When too much ether is given respiration becomes depressed before the heart. These effects make ether a "safe" anaesthetic agent. It is a bronchodilator and produces analgesia. It may be used as the sole anaesthetic agent and is capable of producing good abdominal muscle relaxation.

**Disadvantages:** Ether is associated with a slow onset and a slow recovery. It stimulates salivation and is best used with atropine premedication. The vapour is unpleasant to breathe initially and causes irritation of the bronchial tree which may slow down the induction of anaesthesia. The incidence of nausea and vomiting is higher with ether than with other agents. Ether is explosive when mixed with oxygen and is inflammable in air. It may be ignited by a flame or an electrical spark such as those produced by diathermy or static electricity. The ether vapour is inflammable within the patient (lungs, airway or stomach full of vapour) or outside the patient within 25cm of the anaesthetic circuit.
HALOTHANE (Fluothane)
Halothane contains thymol as a stabilizing agent and is stored in dark bottles as it is decomposed by ultraviolet light

**Advantages:** Halothane is a well tolerated, non-irritant potent agent giving rapid induction, low dose maintenance and rapid recovery. There is a predictable, dose-related depression of respiration and cardiac function.

**Disadvantages:** The depression of the cardiovascular system may cause bradycardia, hypotension and a reduction in cardiac output. Halothane sensitises the heart to adrenaline and predisposes the patient to developing arrhythmias. These arrhythmias occur most commonly in patients who are retaining CO₂ or who have an inadequate analgesic component in their anaesthetic. They can usually be managed by supporting the ventilation, reducing the amount of halothane in the inspired gases and supplementing with another analgesic.

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**Table 9-2: Summary of the Actions of Volatile Anesthetics on Various Ion Currents in the Heart and Most Important Side Effects of the Drugs**

<table>
<thead>
<tr>
<th>Target Current</th>
<th>Effect</th>
<th>Anesthetic Gas</th>
<th>Cardiac Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-type Ca²⁺ current</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, sevoflurane</td>
<td>Reduced contractility, shortened AP duration and refractory time</td>
</tr>
<tr>
<td>β-Adrenergic regulation of</td>
<td>Complex</td>
<td>Halothane</td>
<td>Enhanced proarrhythmicity in comparison with sevoflurane?</td>
</tr>
<tr>
<td>L-type Ca²⁺ current</td>
<td>Interference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage-dependent transient</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, xenon</td>
<td>Shortened AP duration, mismatch within the heart</td>
</tr>
<tr>
<td>outward K⁺ current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage-dependent sustained</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, sevoflurane</td>
<td>Delayed repolarization, mismatch of AP duration</td>
</tr>
<tr>
<td>outward K⁺ current</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP-dependent K⁺ current</td>
<td>Enhancement</td>
<td>Isoflurane, sevoflurane</td>
<td>Myocardial preconditioning</td>
</tr>
<tr>
<td>Fast Na⁺ current</td>
<td>Inhibition</td>
<td>Halothane, isoflurane, sevoflurane</td>
<td>Slowed conduction, induction of tachyarrhythmias?</td>
</tr>
</tbody>
</table>

Effects of paramount importance are printed in bold.

Trichloroethylene (Trilene)

**Advantages:** It maintains cardiac output and is inexpensive.

**Disadvantages:** Arrhythmias may occur and adrenaline administration is contraindicated. Trichloroethylene should be protected from light.

**Contraindications:** Never use trichloroethylene in a circle with soda-lime as the toxic compounds phosgene and carbon monoxide are produced.

Nitrous Oxide

Joseph Priestly discovered “dephlogisated nitrous air” (N2O) at the end of the eighteenth Century. N2O was used as an anaesthetic in 1844 by Horace Wells, an American dentist.

During anaesthesia nitrous oxide diffuses into any body cavity which contains gas. This includes air spaces in the gut, middle ear, endotracheal tube cuff and pneumothorax.

Diffusion hypoxia (Fick principle) may occur at the end of anaesthesia when nitrous oxide rapidly leaves the blood and tissues and passes out through the lungs. This may result in a dilution of the oxygen in the lungs for a few minutes and is prevented by administering extra oxygen at the end of anaesthesia.

N2O mildly increases cardiac output or causes no change in CO

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Nodal rhythm and bradycardia during inhalation induction with sevoflurane in infants: a comparison of incremental and high-concentration techniques

*D. H. Green¹, P. Townsend¹, O. Bagshaw² and M. A. Stokes¹,²,∗*
Heart rate and rhythm changes during sevoflurane inhalation induction in 60 healthy, unpremedicated infants were studied. Twelve patients developed nodal rhythm, but no other dysrhythmias were recorded. The onset of nodal rhythm was associated with bradycardia (<80 bpm) in seven out of 12 cases. This study demonstrated a 20% incidence of nodal rhythm irrespective of inhalation technique. Under conditions where a deep level of inhalation anaesthesia is required for relatively short duration, such as paediatric bronchoscopy, nodal rhythm may occur with sevoflurane, although the incidence of this and other dysrhythmias is much less than when using halothane.

The development of nodal rhythm was found to be related to depth of anaesthesia. In addition, immaturity of the autonomic nervous system in infants makes this group particularly susceptible to the effects of volatile anaesthetic agents on cardiac conduction pathways. In a comparison of the incidence and nature of arrhythmias using halothane or sevoflurane in paediatric dental anaesthesia, Holter monitoring detected a high incidence of arrhythmias (48% versus 16%). A loss of atrioventricular conduction in infants may have clinical significance because of the contribution of atrial contraction to stroke volume. This would be particularly important if airway problems and hypoxaemia developed during an inhalation induction, or if the infant were hypovolaemic.

In summary, the use of incremental or high-concentration sevoflurane for anaesthetic induction in unpremedicated infants was associated with a 20% incidence of nodal rhythm. This unexpected finding highlights the importance of using continuous ECG analysis when studying the side effects of volatile agents in young children.
**Intravenous Induction Agents**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Thiopental</th>
<th>Midazolam</th>
<th>Etomidate</th>
<th>Propofol</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>0% to +36%</td>
<td>-14% to -21%</td>
<td>0% to +22%</td>
<td>-6% to +12%</td>
<td>0% to +59%</td>
</tr>
<tr>
<td>MAP</td>
<td>-18% to +8%</td>
<td>-12% to -26%</td>
<td>0% to -20%</td>
<td>0% to -47%</td>
<td>0% to -40%</td>
</tr>
<tr>
<td>SV</td>
<td>0% to +19%</td>
<td>0% to -20%</td>
<td>0% to -17%</td>
<td>-9% to -25%</td>
<td>0% to +33%</td>
</tr>
<tr>
<td>PAP</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>0% to -17%</td>
<td>-4% to +6%</td>
<td>+44% to +47%</td>
</tr>
<tr>
<td>LAP</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>0% to +27%</td>
<td>—</td>
<td>0% to +33%</td>
</tr>
<tr>
<td>CA AP</td>
<td>Unchanged</td>
<td>0% to -25%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>LVED / LVED</td>
<td>—</td>
<td>—</td>
<td>0% to -11%</td>
<td>+13%</td>
<td>Unchanged</td>
</tr>
<tr>
<td>RV</td>
<td>0% to +33%</td>
<td>Unchanged</td>
<td>Unchanged</td>
<td>-8% to -21%</td>
<td>+15% to +33%</td>
</tr>
<tr>
<td>SV</td>
<td>0% to -24%</td>
<td>0% to -25%</td>
<td>0% to +14%</td>
<td>-6% to -28%</td>
<td>0% to +42%</td>
</tr>
<tr>
<td>SW</td>
<td>-12% to -35%</td>
<td>0% to -18%</td>
<td>0% to -15%</td>
<td>-8% to -18%</td>
<td>0% to -21%</td>
</tr>
<tr>
<td>LSW</td>
<td>0% to -26%</td>
<td>-28% to -42%</td>
<td>0% to -27%</td>
<td>-15% to -40%</td>
<td>0% to +27%</td>
</tr>
<tr>
<td>LVED</td>
<td>NR</td>
<td>-41% to -57%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>TPR</td>
<td>-14%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Unchanged</td>
</tr>
<tr>
<td>TEP</td>
<td>-18% to -28%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NR</td>
</tr>
</tbody>
</table>

Intravenous induction agents are negative inotropes (decrease the force of contraction of the heart). This means they cause BP to decrease.

**Propofol**: produces dose-dependent cardiovascular and respiratory depression, leading to decreases in systemic blood pressure. These effects can be minimized if propofol is injected slowly with sufficient time allowed to achieve the full effect of the dose.

Given its capacity to induce hypotension and bradycardia, it should be used cautiously in hypovolemic patients, and neonates and elderly patients due to their lower compensatory capacity.

**Thiopentone**: decreases cardiac output by a direct negative inotropic action. It decreases the force of the contractions by decreasing ventricular filling which results in increases venous capacity. Causes dose-dependent hypotension and myocardial depression.

**Midazolam**: causes only small haemodynamic changes.
**Etomidate**: Cardiostable, i.e. changes haemodynamic variables the least. Often used with cardiac patients due to its remarkable haemodynamic stability. Etomidate causes cortisol inhibition. (Cortisol is an adrenal hormone which stimulates the conversion of proteins to carbohydrates, raises blood sugar and promotes glycogen storage in the liver). This is a section 29 drug.

**Ketamine**: the drug of choice with patients who are already haemodynamically compromised such as a shocked patient on the battlefield. Needs to be combined with adequate levels of fluid resuscitation. Can cause hypertension and tachycardia. Best avoided in patients with ischaemic heart disease.

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**OPIOIDS**

Thomas Sydenham, the 17th-century pioneer of English medicine wrote: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium". Although opium is no longer regarded as a universal analgesic, it is still very important as the source of morphine.

Morphine is the prototype of opioid anaesthetics. It was used briefly in the late nineteenth century, combined with scopolamine (which acts as an antimuscarinic like atropine), as a complete anaesthetic. However, it was abandoned because of the number of deaths associated with its use. In the late 1960’s morphine in large
doses was reintroduced. In the 1970’s the side effects of morphine anaesthesia became clear.

- Patients anaesthetised with large doses of morphine frequently developed tachycardia.
- Hypotension can occur after even small doses of morphine and is primarily caused by a histamine release resulting in a decrease in SVR. This release is reduced by slower administration of morphine.
- Morphine is not associated with myocardial depression. However, when nitrous oxide given with morphine significant drops in heart rate and BP can result.

**Fentanyl** has been used in anaesthesia for nearly 50 years.

In 1978 T.H. Stanley first introduced Fentanyl as the primary anaesthetic agent. Its use was accompanied by minimal response to stressful stimuli and more haemodynamics stability than with morphine. Large-dose Fentanyl anaesthesia (50 to 75 µg/kg), with 100% oxygen has no significant effect on ventricular function.

- Fentanyl rarely causes hypotension as unlike morphine, Fentanyl does not cause histamine release or vasodilation.
- Can cause bradycardia due to central vagal stimulation.
- Fentanyl prolongs the duration of the cardiac action potential
- The addition of nitrous oxide to fentanyl can result in ventricular depression, tachycardia and a decrease in cardiac output.
- The addition of benzodiazepines with fentanyl can decrease cardiac output and mean arterial pressure.

Fentanyl is significant in cardiac surgery anaesthesia.

The main cardiovascular effect of IV opioids is to attenuate central sympathetic outflow. Sympathetic over activity increases the risk of ventricular tachycardia

**In Conclusion:** As time goes by newer pharmaceutical agents are slowly replacing the historical agents allowing us to anaesthetise with less risk to the patient. Anaesthetic pharmacology though still presents anaesthetists with many multifaceted challenges in choosing appropriate agents for each patient.
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