THE EFFECTS OF ANAESTHETIC AGENTS ON THE CARDIOVASCULAR SYSTEM: A REVIEW¹

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IN WILLIAM HARVEY'S² GREAT WORK, *De motu cordis* (1628), we may read how he was led to his conclusions about the circulation of the blood by *exact observations*, *exact experiments*, and *exact thought* (1). The 300 years since his time have brought forth new techniques and new devices for the investigation of the circulation and heart function (2-8). However, there is still no substitute for the three great components of Harvey's method if the anaesthetist wishes to determine how anaesthetics affect the heart, for we still do not have a clear picture of the many factors involved in normal heart function and how these are affected by stress, disease, and anaesthesia (9, 10, 11).

The key role of the heart is that of a *unidirectional pump*. This pump supplies the motive force of venous blood to the lungs and of 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 per cent of the total blood flow.

The ideal measurement of heart function would be its power, or work per unit of time. However, we can only measure with ease the resistances which the heart must overcome to force the blood into the various regions of the body. These resistances consist mainly of: (a) the viscosity of the blood which affects blood flow; (b) the distensibility of blood vessels which affects peripheral resistance; (c) the inertia of the blood which affects myocardial contractility. And these three are related thus:

$$\text{Peripheral resistance} = \frac{\text{Mean arterial blood pressure}}{\text{Blood flow/unit time}}$$

These resistances constitute the venous and arterial blood pressure. This is the pressure (measured in mm. Hg) exerted by the blood on the walls of the vessels in which it is flowing.

(a) The *viscosity of the blood* or its internal friction varies with the haematocrit. It takes approximately five times the force (dynes/cm./sec.) to move a volume of blood in a tube a certain distance as to move water the same distance. The major part of the heart's energy is required to overcome viscous resistance. *Remember*: haematocrit increases during anaesthesia; plasma volume falls and red cell volume increases (relatively).

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(b) *Distensibility of the vessels* is the relation between changing volume and changing pressure, and is somewhat analogous to the compliance of the lung. There is a tremendous difference between the distensibility of the veins and the distensibility of the arteries. In the dog, there are approximately 700 ml. of blood on the venous side of the circulation at a mean pressure of 7 mm. Hg, whereas on the arterial side there are about 200 ml. at a mean pressure of 100 mm. Hg. The veins can alter their distensibility tremendously, whereas the arteries can only change by a multiple of 4.

This difference is clinically significant when one considers that the vascular volume changes with blood loss. As haemorrhage progresses, distensibility is reduced progressively in the veins and arteries. This reduction in vascular volume is induced by the sympathetic nervous system and circulating catechol amines; and compensates for reduced blood volume enough to maintain an adequate blood flow. When irreversible shock begins, distensibility increases—especially on the venous side. Thus, a very large volume of blood can be injected without clinical response because the blood may merely distend the veins and will not reach the “pump.”

Remember: as anaesthesia deepens, we always see increasing *distension of the veins* due to loss of peripheral venous tone. This eventually reduces the return of blood to the heart.

(c) *Inertia of the blood* means the persistence of the blood in its state of rest, or uniform motion that requires force to accelerate. At the end of cardiac diastole, the blood in the heart exerts an enormous amount of energy in a very short time (.04 sec.) to get this flow started. This powerful thrust is transmitted to the aorta, and can be observed in the recoil of the whole body on the ballistocardiograph. *Remember:* as anaesthesia deepens, this cardiac power is progressively reduced.

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. 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.

SPECIFIC EFFECTS OF ANAESTHETICS ON THE HEART

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.

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.

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 poisons. 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 haemodynamic 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; atropine, epinephrine, methoxamine and cedilanid
- Blood volume (plasma and cells) and venous haematocrit
- Arterial oxygen saturation, pH, $p\text{CO}_2$, and oxygen consumption
- Cardiac output and stroke volume (dye or rhisa)
- Force of myocardial contraction (strain gauge bridge)

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 (Fig. 1).

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 in the major organs in the body. In the presence of heart disease, all cardiovascular changes caused by anaesthesia are aggravated.

FIGURE 1

SPINAL ANAESTHESIA (12-16)

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 paralyzes 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* (Fig. 2).

Sympathetic block at the pre-ganglionic level affects vasomotor tone of the arterioles, which accounts for 60 per cent of the systemic peripheral vascular resistance. The other 40 per cent is maintained by capillary and venous blood flow.

Blood pressure. A fall in arterial blood pressure is the most frequent immediate effect of spinal anaesthesia. Many theories have been offered as to the aetiology: haematogenous intoxication; denervation of adrenal glands; reduced tone of skeletal muscles, venous dilatation, and pooling of blood; direct paralysis of vasomotor and respiratory centres; hypotension—secondary to respiratory insufficiency; and so on.

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

FIGURE 2

proportion to the number of sympathetic fibres blocked. Spinal anaesthesia given after total sympathectomy produces no change in blood pressure.

Clinically, hypotension does not become marked until the sensory block extends above the costal margin. It was believed that this hypotension was due to the splanchnic block, with pooling of blood in the abdominal viscera, but it has been shown clinically and experimentally that there is no excessive pooling in this area.

The mechanism of hypotension due to sympathetic paralysis by spinal anaesthesia is now explained in two ways. First, the generalized arterial and arteriolar dilatation causes a decrease in peripheral vascular resistance, which is great enough to account for the major portion of the hypotension. Secondly, hypotension is secondary also to a decrease in cardiac output, as a result of peripheral pooling and diminution of venous return to the heart.

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. If vasoconstrictors are administered to maintain peripheral resistance, but hypotension still occurs, then it is due mainly to a fall in cardiac output. Relatively minor degrees of hypotension are mainly the result of changes in peripheral resistance, but if the pressure continues to fall below a critical level, fall in cardiac output is responsible. This can be illustrated when total subarachnoid sympathetic block is given to a normal

patient: systolic blood pressure will fall from 120 to 90 if venous return and cardiac output are maintained by head-low position. If the horizontal or head-up position is then taken, gravitational pooling will reduce venous return and cardiac output, resulting in abrupt severe hypotension.

Pulse rate. Bradycardia may be seen. This varies directly with the height of anaesthesia. It is partly attributed to paralysis of the pre-ganglionic cardiac accelerator fibres (T_1-4), leaving control of the cardiac pacemakers to the inhibitory vagal effect. It is related also to the degree of arterial hypotension.

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.

Theoretically the hypotension of spinal anaesthesia should cause tachycardia, reflexly mediated through the pressor-receptors of the carotid sinus and aortic arch. However, the Bainbridge reflex may be dominant over those of the pressor-receptors and the efferent arc of reflexes from T_1-4 may be blocked by the anaesthesia (afferent arc is parasympathetic in origin and is unaffected).

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 paralysed, 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.

Remember. After spinal anaesthesia has stabilized, the peripheral resistance usually remains constant, and changes in blood pressure are then due to alterations in cardiac output or circulating blood volume. These are corrected by posturing, blood transfusion, or increasing myocardial tone with a vasopressor such as ephedrine. When respiration is very depressed, artificial respiration with intermittent positive pressure may further lower the blood pressure if venous return is not assisted by head-low posture. Positive-negative pressure breathing may be helpful under these circumstances.

Stroke volume. 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 anaesthesia 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. In each case the diminution of venous return to the heart is approximately the same, but spinal anaesthesia causes bradycardia, while the others cause tachycardia. Since diastole is shortened during tachycardia, the volume of blood in the ventricles at the start of systole (that is, potential stroke volume) is less during tachycardia than during bradycardia.

Myocardial power and ventricular force. The power of the heart 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 the reduced end-diastolic blood volume is associated with a corresponding decrease in the force of myocardial contraction; sympathetic paralysis, involving fibres to the adrenal glands, may lower the catechol amine 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.

Myocardial irritability. Specific investigations have not been carried out, but spinal anaesthesia possibly reduces irritability because it reduces the blood level of catechol amines.

Coronary blood flow. 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.

It has been shown that coronary blood flow decreases during high spinal anaesthesia. This fall is not the same in extent as the fall in mean aortic blood pressure and the oxygen requirements of the myocardium. The coronary flow, therefore, remains quite adequate, provided that the vessels are free from atheromatous plaques and other pathological changes which might initiate thrombosis and myocardial infarction.

Remember. Even though depression of the arterial blood pressure during spinal anaesthesia varies mainly with the height of the sympathetic block (peripheral dilatation) and with cardiac output, the amount of trauma and manipulation to

which a patient is subjected after induction of anaesthesia, and certain constitutional factors such as hypertension, old age, hypovolaemia, and pregnancy, also play an important role. In addition, when hypovolaemia is due to active bleeding, the induction of spinal anaesthesia may accelerate the loss of blood by producing vasodilatation in the bleeding area.

Summary. Spinal anaesthesia may have three circulatory effects: decrease of the total of 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.

DIETHYL ETHER (17-20)

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 (Fig. 3).

FIGURE 3

Pulse rate usually increases slightly owing to paresis of the vagal inhibitory mechanism, augmentation of cardiosympathetic 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 falls 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. 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.

ECG. Heart block and ectopic beats are rare during light ether anaesthesia, but as narcosis becomes very deep, they may begin to appear. Arrhythmias due to ether anaesthesia are exceedingly uncommon in humans, and the heart is very resistant to abnormal excitation by catechol amines.

Most laboratory data indicate that ether is a myocardial depressant, but in man the sympathetic stimulation or liberation of catechol amines produces a positive inotropic effect on the heart that overcomes the depressant influence of ether on the myocardium if the patient is healthy.

CYCLOPROPANE (21-26)

The main difference between ether and cyclopropane lies in the severe respiratory depression that surgical depths of anaesthesia produce with the latter. When adequate artificial respiration is provided, the cyclopropane content of the blood can be increased to a level of about 20 per cent 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 (Fig. 4).

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 premedication.

Cyclopropane has less effect on the peripheral 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.

Pulse rate is slowed slightly below resting levels, but the effect on the heart rate is not striking. Low pulse rates which are seen have been attributed to a pulse deficit due to ectopic beats. The slowing of the pulse rate therefore is not necessarily a sign of increasing depth.

FIGURE 4

Blood pressure. There is no significant alteration in blood pressure during surgical planes of cyclopropane anaesthesia if pulmonary ventilation is adequate. Hypertension that occurs is probably due mainly to the effect of hypercarbia, and is also due to emergence from deep to light levels of anaesthesia. Sensory stimulation, coughing, and intubation at light levels also cause hypertension.

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

Cardiac output. 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 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.

ECG. A rising $p\text{CO}_2$ in the arterial blood increases the incidence of ectopic beats. Spontaneous arrhythmias are not common when pulmonary ventilation is adequate. When they occur, augmenting respiratory exchange, reducing the concentration of cyclopropane in oxygen, and administering a barbiturate have been used successfully for treatment. The heart becomes extremely irritable when catechol amines are injected during cyclopropane anaesthesia. This may be seen on the electrocardiogram by the progressive appearance of a nodal rhythm and ventricular extrasystoles, ventricular tachycardia, and multifocal ventricular extrasystoles leading to auricular and ventricular fibrillation.

TRICHLORETHYLENE (27, 28, 29, 30)

This agent is very toxic to the heart when used as a total anaesthetic as cyclopropane is used. 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-oxygen (3:1 or 2:1), meperidine, and muscle relaxants, it provides excellent analgesia and hypnosis, and a very smooth anaesthetic course with less than 0.5 per cent (Fig. 5).

FIGURE 5

In clinical use with supplements, it has little effect on blood pressure or pulse rate, causes moderate peripheral vasodilatation, but, 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. 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.

Ventricular fibrillation with epinephrine is highly likely during anaesthesia with trichlorethylene. For prolonged anaesthesia 0.5 per cent should NOT be exceeded.

CHLOROFORM (31, 32, 33)

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 (Fig. 6). When this agent is used for major procedures, an accurately calibrated vaporizer should be employed to control its rate of administration.

Full atropinization combined with a phenothiazine derivative such as perphenazine (5 mg. intramuscularly) or levomepromazine (10 mg. intramuscularly) should be used for premedication, to precede a smooth induction with a sleep dose of thiopental. It is best to use dimethyl d'tubocurarine or succinylcholine to accomplish endotracheal intubation. Thereafter, respiration should be controlled in a non-rebreathing system and anaesthesia maintained with nitrous oxide-oxygen (2:1) and less than 1.5 per cent chloroform for the robust, young, healthy patient and less than 1.0 per cent for the debilitated patient. If muscular relaxation is sometimes not adequate, small doses of a muscle relaxant should be added rather than increasing the concentration of chloroform administered to exceed the above-noted limits.

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. With prolonged anaesthesia, 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.

Cardiac output falls with excessive chloroform anaesthesia owing to the depression of myocardial tone and ventricular force.

Myocardial excitability. Under light chloroform anaesthesia, 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 effect of epinephrine on the heart during chloroform anaesthesia is less than that seen with a corresponding surgical plane of anaesthesia with cyclopropane, Fluothane, and trichlorethylene, but it is dangerous nevertheless.

FLUOTHANE (34, 35, 36, 37)

Fluothane has a characteristic action on the heart and circulation which in man 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 slightly less potent as a hypnotic.

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. 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.

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.

Myocardial irritability. 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. Arrhythmias may occur during rapid induction and during deep anaesthesia, but usually disappear if the concentration of Fluothane is reduced, if ventilation is improved, and if atropine is administered. In experiments with dogs, ventricular fibrillation is easily produced during light Fluothane anaesthesia if epinephrine is injected (Fig. 6).

FIGURE 6

FLUOTHANE-ETHER AZEOTROPE (38, 39, 40, 41)

The effect of Fluothane on the heart is reduced significantly when Fluothane-ether azeotrope (68.3:31.7 by volume) is employed (Fig. 2). Blood pressure is affected less with a concentration of the mixture that contains more Fluothane than that which might cause marked hypotension. There is less tendency to

slowing of the pulse rate, and the hypotensive response to d'tubocurarine is not seen as frequently. There is moderate reduction in peripheral resistance and in myocardial tone, so that cardiac output does not fall as rapidly with increasing depth of anaesthesia.

Myocardial irritability is also less with the mixture than with Fluothane alone, so that spontaneous arrhythmias are not common if ventilation is adequate, and ventricular fibrillation is far less likely to occur with the injection of epinephrine.

Satisfactory anaesthetic conditions for major operations with little myocardial depression are seen when less than 1.5 per cent of the mixture is used with nitrous oxide-oxygen (2:1) and a muscle relaxant in a non-rebreathing system and with augmented respiration.

INTRAVENOUS BARBITURATES (42, 43, 44)

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). 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 (Fig. 7).

Blood pressure. 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

FIGURE 7

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.

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.

When artificial respiration with adequate oxygen is provided, very much larger doses of barbiturates are well tolerated.

ECG. 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.

PROCAINE, LIDOCAINE, AND RELATED ESTERS (45, 46, 47)

When administered intravenously, procaine, lidocaine, and their related esters have an action on the heart which is similar to that of quinidine. 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. 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.

ECG. Procaine prolongs the PR interval and QRS complex. Excessive doses may cause premature beats, tachycardia, and ventricular fibrillation.

EFFECT OF NARCOTIC ANALGESICS ON THE HEART (48, 49)

When narcotic analgesics (morphine, meperidine, alphaprodine, dipipanone HCl) are administered intravenously in therapeutic doses, there is probably a very mild depressant effect on the healthy heart. The change in circulatory dynamics is related mainly to the general physical condition of the patient and to the rate, concentration, and dose administered (Fig. 8).

Blood pressure. Hypotension may occur immediately after an intravenous injection, probably because of peripheral vasodilatation (direct action on the

FIGURE 8

vessels), by central vasomotor depression, and perhaps by ganglionic blockade. In the healthy subject, blood pressure is rapidly restored, but in debilitated patients hypotension may persist if it is not treated.

Pulse rate decreases momentarily after meperidine. This may be followed by tachycardia which is prolonged. This is said to be due to its vagolytic action. Morphine may cause slight bradycardia.

Myocardial contractility as measured by strain gauge arch experiments show a brief decrease, followed by a moderate increase in contractility accompanying the period of hypotension with meperidine.

MUSCLE RELAXANTS (50, 51, 52)

These drugs have no significant direct effect on the heart. However, d'tubocurarine may cause some ganglionic block which is seen best when a large dose is injected rapidly during anaesthesia. This will cause hypotension. Flaxedil apparently produces a selective block of the vagus, which results in tachycardia, without change in the blood pressure. Succinylcholine in relatively large doses frequently causes severe bradycardia in infants and young children, which may be reversed with atropine.

PHENOTHIAZINE DERIVATIVES (53, 54)

The main cardiovascular effects of the parenteral administration of most of the phenothiazine derivatives (for example, chlorpromazine) are similar in many

ways to the effect of a high spinal anaesthetic, in which sufficient dilution of the local anaesthetic agent was employed to produce only light sensory anaesthesia. There is a decrease in peripheral vascular resistance which results in hypotension and tachycardia. These may be increased or decreased by posturing. Peripheral blood flow is increased two to four times with chlorpromazine.

The ECG may show an initial sinus arrhythmia, which disappears after a short while.

Myocardial irritability and automaticity are reduced, and there is a greatly reduced positive inotropic response to epinephrine and other vasopressors. Phenothiazines protect the heart against ventricular fibrillation due to epinephrine with chloroform, cyclopropane, trichlorethylene, Fluothane and Fluothane-ether when administered beforehand.

Cardiac output is not reduced by the phenothiazines unless very marked hypotension is produced by the head-up posture. Coronary blood flow is increased by chlorpromazine.

HYPOTHERMIA (55, 56, 57)

The effect on the heart of moderate total body cooling (28 to 30° C.) is still the subject of extensive study. Myocardial function is depressed by lowered temperature, but the depression is not the same as that associated with the response to anaesthetic or narcotic drugs (Fig. 9).

FIGURE 9

Drug depression implies that myocardial contractility is altered. It is more gradual, the amplitude is lower, the duration is shorter and the stroke volume is reduced. There is also an elevated end-diastolic ventricular pressure. During total

body cooling the only changes in heart action are the more gradual contraction and the lowered amplitude of contraction.

Blood pressure falls slowly during cooling after an initial elevation that is caused by intense vasoconstriction.

Pulse (heart) rate slows to a greater degree than the fall in blood pressure. The bradycardia induced by cooling the heart differs from that caused by vagal stimulation in that the absolute duration of systole and isometric relaxation increase by 250 to 300 per cent, during hypothermia, whereas systole increases only 50 per cent and isometric relaxation does not change at all with vagal slowing.

Stroke volume remains close to the normal, coronary blood flow and oxygen uptake appear to remain adequate, while cardiac output and work of the heart are reduced during hypothermia.

If the body temperature is allowed to fall below 28° C., the myocardium becomes very irritable and ventricular fibrillation is likely, even when oxygenation and carbon dioxide elimination are satisfactory.

OTHER FACTORS ASSOCIATED WITH ANAESTHESIA THAT AFFECT THE HEART (58-61)

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 standstill follows quickly.

Acidosis

The effects of metabolic and respiratory acidosis are not usually evident during anaesthesia, but they may be added to those of hypoxia. The cardiac output decreases as hypercarbia develops, but the output may be restored to normal with the catechol amines. The depressant effect of acidosis on the heart is due mainly to the fall in pH, because buffering the pH back to 7.40 in the presence of hypercarbia restores the myocardial force.

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.

Induced Hypotension (62, 63)

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 80 mm. Hg 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 (Fig. 10).

FIGURE 10

Airway Pressure (64-73)

The circulatory effect of positive pressure in the airway has been known for almost a century. Detailed studies have been carried out by many in recent years, and all have shown that whenever air, anaesthetic gases, or vapours are forced into the lungs, there is interference with the circulation if the mean airway pressure is permitted to rise. This interference is especially marked when the patient has a reduced circulating blood volume. 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. 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.

Abnormal Cardiac Rhythms (74-82)

Abnormal cardiac rhythms may develop during anaesthesia. 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, catechol amines). Hypoxia, hypercarbia, elevated blood potassium, and a variety of external stimuli also cause abnormal cardiac rhythms. 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.

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. The addition of ether vapour is very helpful with cyclopropane and with Fluothane. Atropine intravenously to block efferents and procaine locally to block afferents are also helpful. In some cases, quinidine, procaine amide, chlorpromazine, or perphenazine may be given intravenously to depress myocardial irritability, particularly for the treatment of paroxysmal ventricular tachycardia and ventricular extrasystoles.

RÉSUMÉ

Le rôle principal du cœur est celui d'une pompe unidirectionnelle. Environ 80% du courant sanguin qui passe au cœur est dirigé vers quatre organes vitaux: le cerveau, le foie, le rein et le muscle cardiaque.

On ne peut mesurer la fonction cardiaque qu'indirectement, en mesurant les résistances que le cœur doit vaincre. Parmi ces résistances, il faut mentionner: la viscosité du sang qui modifie le courant sanguin, l'extensibilité des vaisseaux sanguins qui change la résistance périphérique et, enfin, l'inertie du sang qui influence la contractilité du myocarde. Toutes ces résistances sont influencées par l'anesthésie: d'abord, l'hématocrite augmente (la viscosité augmente), l'extensibilité diminue (la résistance périphérique diminue) et la contraction du myocarde diminue (le débit systolique et le débit cardiaque diminuent).

Une autre conception importante en anesthésie est la relation entre la résistance artérielle et la résistance veineuse. Les modifications de cette relation ne sont pas sans influencer la pression de perfusion du cerveau, du cœur, et du rein et, plus spécialement, au cours de l'anesthésie profonde, durant l'hypothermie et l'hypotension provoquée avec l'emploi d'agents ganglioplégiques. Lorsque la résistance artérielle augmente, la pression artérielle s'élève sans grande modification du débit cardiaque; par contre, lorsque la résistance veineuse augmente, la pression artérielle et le débit cardiaque tombent à pic. D'autre part, une augmentation proportionnelle des deux résistances: artérielle et veineuse n'abaisse pas la pression artérielle, mais le débit cardiaque subit une légère diminution.

Lorsque les parois vasculaires sont normales, la résistance préartériolaire compte pour environ 5 à 15% de la pression aortique. Au cours d'une hémorragie et d'une anesthésie profonde, la résistance préartériolaire augmente et peut compter jusqu'à 50% de la pression aortique. Dans ces éventualités, le cœur

emploie la moitié de son énergie pour pousser le sang dans les artérioles. La perfusion tissulaire devient alors considérablement réduite.

Quels sont les effets spécifiques des agents anesthésiques sur le cœur?

Il est difficile d'être positif sur la sécurité relative d'un agent anesthésique en tenant compte de son action sur le cœur parce que cette sécurité tient davantage à l'habileté avec laquelle l'agent est donné ainsi qu'aux mesures thérapeutiques que l'anesthésiste prudent emploie qu'aux propriétés inhérentes de n'importe quel agent anesthésique.

L'effet cardiovasculaire de tout agent dépend principalement de sa voie d'administration, de sa vitesse d'injection et de sa concentration selon que le malade respire spontanément ou que sa ventilation est augmentée, selon la profondeur et la durée de l'anesthésie et selon l'état physique général du malade—en attachant une importance spéciale à la fonction cardiopulmonaire préanesthésique et au volume du sang circulant.

L'effet des agents anesthésiques sur l'hémodynamique demeure spécialement difficile à préciser à cause du fait que la circulation normale engendre toujours des réflexes circulatoires et apporte dans la circulation des substances endogènes sécrétées en réponse à l'injection des poisons. Chacun agit sur une partie différente de la dynamique circulatoire pour éviter un changement général. Il s'impose, en conséquence, d'enregistrer simultanément autant de facteurs variables que possible. Ces facteurs variables nous procurent des indices plus fiables dans tout le cadre affecté et le sens des changements. *Il est rarement possible de tirer des conclusions sur les mécanismes des effets circulatoires d'un médicament à la suite des changements qu'il peut produire sur un seul facteur variable tel le débit cardiaque.* Pour ce qui concerne l'hémodynamique, tous les paramètres cardiorespiratoires devraient être enregistrés.

C'est encore la mesure directe de la tension artérielle qui, comme seule mesure, demeure la plus importante parce que:

(a) Le débit ventriculaire droit, en définitive, peut être apprécié par le débit ventriculaire gauche et la tension artérielle, ce qui donne une idée du retour veineux:

(b) Les effets circulatoires, en général, apparaissent précocement sur la tension artérielle.

(c) On peut y suivre les réponses instantanées de battement en battement.

Il existe certains effets spécifiques reconnus que chaque agent produit sur le cœur—ou bien directement sur sa force de contraction et sur son excitabilité ou bien indirectement en libérant des hormones endogènes—épinéphrine, norepinéphrine, acetylcholine, histamine ou sérotonine; ou encore en changeant le tonus veineux périphérique qui affecte le retour du sang au cœur; ou encore en déprimant la respiration, ce qui entraîne de l'hypoxie myocardique et de l'acidose.

En général, toute dépression respiratoire par un agent anesthésique entraîne d'abord une augmentation de la force de contraction du myocarde—suivie après d'une diminution progressive. Cette diminution progressive de la force de contraction du myocarde accompagne habituellement l'approfondissement de l'anesthésie chirurgicale, peu importe l'agent employé. L'état de vasoconstriction

observé avant l'induction de l'anesthésie fait place rapidement à une augmentation du volume de sang circulant périphérique à mesure que s'approfondit l'anesthésie. Cela s'accompagne également d'une diminution du volume de sang circulant dans les principaux organes de l'organisme. Quand il existe des pathologies cardiaques, tous les changements cardiovasculaires causés par l'anesthésie sont aggravés.

La rachianesthésie agit sur le cœur de trois façons à cause de la paralysie des fibres sympathiques vasomotrices au niveau préganglionnaire. Il se produit d'abord une diminution de la résistance périphérique totale par interruption des influx vasoconstricteurs aux artérioles; il s'ensuit une accumulation de sang dans la circulation veineuse, conséquence de la dilatation postartériolaire, ce qui diminue le retour veineux au cœur; enfin, le débit cardiaque diminue à cause du ralentissement du cœur.

L'éther diéthylique n'a pas d'effet marqué sur le cœur normal parce qu'une libération de catécholamines, dès le début, maintient l'homéostasie cardiovasculaire. Si l'on recourt à de l'anesthésie profonde ou prolongée, il se produit une dépression progressive du myocarde et de la circulation périphérique.

Le cyclopropane agit beaucoup moins sur la circulation périphérique que l'éther diéthylique et il exerce peu d'effet dépresseur sur le cœur si la ventilation pulmonaire est maintenue adéquate. Toutefois, le cyclopropane est très irritant pour le système de conduction du cœur et il entraîne des arythmies sérieuses durant l'anesthésie profonde ou si des catécholamines entrent en circulation. Le trichlorethylène est également très irritant pour le cœur; il ne devrait pas être employé comme agent anesthésique primaire sans avoir une source d'atmosphère suffisante pour réduire la concentration inhalée à moins de 1%. Le chloroforme et le Fluothane peuvent également agir sérieusement sur la fonction cardiaque en produisant directement une dépression myocardique par stimulation vagale et par de sérieuses arythmies ventriculaires lorsque des catécholamines entrent en circulation. Si ces substances anesthésiques sont employées en faible concentration avec une ventilation assistée et que le malade reçoit des doses thérapeutiques d'atropine, elles n'ont pas d'effets sérieux sur le cœur. Le mélange azéotropique Fluothane-éther produit sur le cœur des effets semblables à ceux du Fluothane et du chloroforme mais ces effets sont beaucoup moins marqués. La procaine et la Xylocaïne dépriment la conduction dans le myocarde de façon semblable à celle de la quinidine et ils rendent le cœur moins sensible aux stimuli. De grandes doses de ces médicaments réduisent la force de contraction du myocarde et peuvent entraîner une hypotension marquée.

Les barbituriques intraveineux ont peu d'effets dépresseurs sur le cœur normal et sur la circulation périphérique à moins qu'on les administre rapidement ou à fortes doses. On peut affirmer la même chose des narcotiques analgésiques et des myorésolutifs qu'on administre par les veines. Les dérivés puissants du phénothiazine n'exerce que peu d'effet direct sur le cœur mais ils agissent sur la circulation en diminuant le tonus vasculaire périphérique, produisant de l'hypotension, de la tachycardie et une augmentation du volume de sang circulant périphérique.

Il existe d'autres facteurs qui, s'ils sont ajoutés à l'anesthésie, agissent sur le cœur de la façon suivante:

L'hypothermie légère produit une diminution plus graduelle et plus marquée de l'amplitude de contraction du cœur. Cela diffère de la dépression médicamenteuse qui raccourcit également la durée de la contraction et entraîne une élévation de la pression ventriculaire à la fin de la diastole. Une hypothermie plus prononcée augmente l'irritabilité myocardique au point de conduire à la fibrillation ventriculaire.

Une hypoxie légère et de courte durée augmente la contractilité myocardique. Pour peu qu'elle se prolonge, surtout s'il existe une dépression sympathique, la contractilité myocardique diminue très rapidement.

L'acidose (respiratoire et/ou métabolique) diminue la contractilité myocardique à cause de l'abaissement du pH. S'il existe des pathologies cardiaques, les effets dépresseurs de l'hypoxie et de l'acidose sont beaucoup plus manifestes.

L'hypotension provoquée entraîne un écart entre le colume de sang circulant et la capacité du lit vasculaire. Cela n'affecte pas le cœur si le retour veineux est augmenté et si la pression sanguine n'est pas abaissée au-dessous du niveau de la pression de perfusion nécessaire requise par les organes vitaux.

Une élévation de la pression moyenne de l'atmosphère produite en augmentant la ventilation durant l'anesthésie déprime la fonction cardiaque en retardant le retour du sang veineux. Les effets dépresseurs sur le cœur sont d'autant plus marqués que le malade possède un volume de sang circulant réduit.

Au cours de l'anesthésie, on peut observer des rythmes anormaux. Ils s'observent habituellement à la suite de l'effet direct de certains médicaments sur le cœur, médicaments qui peuvent raccourcir la période réfractaire, déprimer le potentiel électrique de repos ou encore modifier la sécrétion de substances endogènes qui affectent le cœur (e.g., catécholamines). L'hypoxie, l'hypercarbie, un taux de potassium sanguin élevé et une variété de stimuli externes peuvent également conduire à des rythmes cardiaques anormaux. Une stimulation ou une traction sur les hiles, les côtes, l'estomac, l'incision d'une plèvre malade, du péricarde, une pression mécanique sur le vague ou sur le sinus carotidien ou encore la manipulation ou la rotation d'un cœur malade, tous ces gestes sont susceptibles de produire de sérieuses arythmies.

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