ORGAN PERFUSION DURING CONTROLLED HYPOTENSION

LEO STRUNIN

Relatively short periods of unwanted hypotension, such as those associated with “shock” states, may be followed by irreversible organ damage. In contrast, controlled hypotension is rarely followed by organ damage, although minor reversible changes in function may occur (Rollason and Hough, 1960; Enderby, 1961; Linacre, 1961). The usual explanation for this paradox is that in the former situation hypotension is accompanied by severe decreases in organ blood-flow, with associated acid-base and metabolic changes, whereas with deliberate hypotension organ blood-flow is well maintained and the other changes do not occur. Clearly, even under controlled conditions, there must be some arterial pressure at which organ flow is no longer adequate. Indeed, the question is commonly asked, “What reduction in arterial pressure is safe?” In fact, what is really required is the answer to the question, “Is the flow adequate?” When considering individual organs, measurement of blood-flow is difficult, and in the main the techniques are only practical under somewhat artificial conditions, or are confined to animal studies. The practical anaesthetist, therefore, has relied on measuring systemic arterial pressure, and after accepting some value as “normal” has assumed that the individual pressures and therefore perfusion of the various organs in the body is adequate. It does not necessarily follow that the perfusion of an individual organ is reflected in the systemic arterial pressure even if one assumes, perhaps incorrectly, that the pressure there is indeed related to flow.

Many organs in the body such as the brain, kidney, skeletal muscle and intestine exhibit “autoregulation”. That is, they maintain their perfusion over a wide range of pressure changes, and it is only when the pressure decreases to relatively low values that adequate perfusion cannot be maintained. This “critical” pressure varies from organ to organ and probably from individual to individual. Autoregulation probably occurs in the absence of nervous control, and three mechanisms have been suggested: first, stretch-myogenic, where the smooth muscle in the vasculature responds to altered tension, that is, arterial pressure; second, passive mechanical, which applies particularly to capsulated organs, where expansion of the organ with increasing pressure compresses thin-walled vessels and leads to an increase in vascular resistance; third, metabolic, where changes in pressure produce vaso-active substances. Anaesthesia tends to abolish autoregulation, and, combined with induced hypotension, may have more marked effects on organ blood-flow than either factor alone. It is very difficult, therefore, to give an answer to the question, “What systemic pressure is safe during anaesthesia?”

It is now intended to examine in more detail how organ perfusion is affected by deliberate hypotension and anaesthesia in the brain, liver, kidney and finally the heart.

THE BRAIN

Lassen (1959) demonstrated that cerebral blood-flow (CBF) remained constant in conscious volunteers over a wide range of mean arterial pressure values (60–150 mm Hg). If hypotension is deliberately induced, cerebral vasodilatation occurs, restoring the blood-flow to normal (Moyer, Morris and Polksmith, 1954). On the other hand, an increase in arterial pressure is followed by cerebral vasocstriction (Hafkenschiel, Friedland and Zintel, 1954). Autoregulation of CBF has some limitation, and below a critical value of arterial pressure adaptation cannot continue further, as maximal cerebral vasodilatation will have occurred. If arterial pressure is further reduced, then this leads to a proportional reduction in CBF. Autoregulation probably varies from individual to individual, and depends to some extent on the patient’s age and the condition of the cerebral vessels. It is probable that the lower limit of mean arterial pressure below which CBF is no longer autoregulating is reached when mean arterial pressure has decreased by about one third (Finnerty, Witkin and Fazekas, 1965). This mean pressure corresponds to a systolic value of about 60 mm Hg. Autoregulation is obviously an important factor when the effects of induced
creases because of vasodilatation. For example, the oxygen tension decreases below normal, CBF in arterial oxygen tension above normal. If arterial For example, inhalation of 100% oxygen reduces range, can produce toxic effects on cerebral function, and should be remembered when hypocapnia is part of an induced hypotensive technique. The combination of hypotension and the cerebral vasoconstrictive effects of a low arterial Pco₂ could be detrimental to cerebral function. Indeed, some anaesthetists prefer spontaneous ventilation both to assess medullary function and to prevent hypocapnia. However, the effect of a low arterial Pco₂ may be offset by that of general anaesthetic agents on the cerebral circulation. In general, these tend to increase CBF by vasodilatation and therefore, when combined with hypotension, may not necessarily cause so severe a decrease in CBF as might be expected from experimental studies of the effects of hypotension with or without hypocapnia (Rood et al., 1974). Boysen and his colleagues (1974) suggested that the critical lowest value of CBF was 18 ml/100 g/min in the normothermic, normocapnic or slightly hypocapnic patient anaesthetized with halothane/nitrous oxide. This CBF corresponded to a carotid artery stump pressure of 55 mm Hg or above.

Changes in arterial oxygen tension also affect cerebral blood-flow (Schmidt, 1950). Since high oxygen tensions, particularly in the hyperbaric range, can produce toxic effects on cerebral function, the brain protects itself by vasoconstriction. For example, inhalation of 100% oxygen reduces CBF by about one-fifth. These changes can be demonstrated from measurements of a constant cerebral venous oxygen tension despite variations in arterial oxygen tension above normal. If arterial oxygen tension decreases below normal, CBF increases because of vasodilatation. For example, the inhalation of 10% oxygen increases CBF by some 30%. It may be, therefore, that the practice of administering high concentrations of oxygen during induced hypotension is not beneficial to cerebral blood-flow, although added oxygen may be necessary to offset the effects of hypotension on pulmonary gas exchange (Eckenhoff et al., 1963a).

CBF is also dependent on intracranial pressure (ICP). The relationship between ICP and CBF is similar to the autoregulation between CBF and arterial pressure. It follows, therefore, that there is some critical value of ICP which will markedly reduce CBF. For example, an increase in venous pressure or a small decrease in arterial pressure during induction of anaesthesia may have detrimental effects on CBF in the patient whose cerebral circulation is critically compromised by increased ICP. These factors should be borne in mind when contemplating hypotensive anaesthesia for neurosurgery in patients with increased ICP.

In this context, temperature may be relevant: hypothermia causes cerebral vasoconstriction and leads to a reduction in CBF; conversely, an increase in body temperature causes cerebral vasodilatation. There is a linear relationship between CBF, cerebral metabolic rate for oxygen, and body temperature. A 10°C decrease in body temperature will reduce flow and metabolic rate by 50% (Eckenhoff, 1974).

We have considered above the direct effect of changes in arterial pressure, arterial Pco₂ and Pao₂, ICP and other factors on CBF. Anaesthetic agents may indirectly affect arterial pressure, and alter arterial Pco₂ and Pao₂ but, in addition, they may have some direct effect on the brain. For example, while it is well recognized that halothane increases CBF, the mechanism was presumed to be a direct vasodilatory effect on the cerebral vessels. Recently, however, Smith (1973b) has suggested that the mechanism may be metabolic. In previous work Smith (1973a) showed that cerebral arteriovenous oxygen content difference varied inversely with the depth of anaesthesia produced by halothane, enflurane and isoflurane. Since in this instance the arterial oxygen content was constant, cerebral venous oxygen content seemed to vary directly with the depth of anaesthesia. Smith suggests that the primary effects of halothane are to decrease cerebral metabolism and then to regulate cerebral venous oxygen content to maintain a favourable cerebral tissue oxygen tension. The changes in CBF then follow passively. At present, however,
the mechanisms whereby halothane, and probably other volatile anaesthetic agents, produce these changes is unknown.

Larson and his colleagues (1974) have recently reviewed the evidence that anaesthetics may protect the brain from acute hypoxia or ischaemia. They contrast the protective effects provided by anaesthetics, perhaps as a result of a decrease in cerebral metabolism, with the somewhat different protective effects seen with hypothermia. It may be that anaesthetic agents protect only the actively functioning neurones, whereas hypothermia protects cerebral function more widely because of a generalized decrease in energy requirements. These authors also point out that regional alterations in CBF, despite a generalized decrease in total CBF, may be more protective than any metabolic depression. If correct, this would imply that the brain may be protected from acute ischaemia by any drugs that decrease CBF or ICP, for example neuroleptanaesthesia, opiates or steroid anaesthetics, provided that normal arterial Pco₂ is maintained. Larson and his colleagues conclude that barbiturates, opiates and neurolept agents may be the anaesthetic agents of choice for patients undergoing operations in which the risks of cerebral ischaemia or oedema are high.

At this point the clinical anaesthetist about to embark on induced hypotension may well feel confused as to the likely effects of his technique on the cerebral circulation. In the end, despite the results of the various studies reviewed above, the most important thing is what happens in the clinical situation during “routine hypotensive anaesthesia”. The investigation at East Grinstead (Eckenhoff et al., 1963b) showed that the risks of brain damage were minimal provided that hypotensive anaesthesia was scrupulously administered. As yet no further study has been published to refute these findings.

THE LIVER

The liver is unique among the body organs in having a double circulation. Most of its blood-flow (about 70%) is via the portal vein and, depending on the degree of gut activity, is at an oxygen content somewhere between that of mixed venous and arterial blood. The remainder of the liver blood-flow (LBF) is supplied from the hepatic artery. The splanchnic circulation (that part of the circulation draining into the portal vein) is richly innervated by the sympathetic nervous system. Therefore, changes in carbon dioxide and oxygen tension and probably pH may change LBF by sympathetic effects, despite there being little or no change in the systemic circulation. In contrast to the brain and kidneys, the liver is not an auto-regulating organ, and a decrease in arterial pressure will lead to a decrease in LBF. In addition, an increase in PaCO₂ (Epstein et al., 1961) or a decrease in PaO₂ will lead to a catecholamine response which causes splanchnic vasoconstriction and therefore a decrease in LBF. Hypocapnia, produced by IPPV, also leads to a decrease in liver blood-flow, probably as a result of the effects of mechanical ventilation (Cooperman, Warden and Price, 1968).

It is of interest that in several animal species (e.g. dog, seal, and raccoon), the outgoing vasculature from the liver contains a considerable quantity of smooth muscle (Mauntner and Pick, 1915). If the liver is subjected to detrimental changes in acid-base balance, hypoxia or hypotension, this smooth muscle goes into spasm and the phenomenon known as venous outflow block (VOB) occurs, LBF being grossly reduced. The surface appearance of the liver is characteristic in VOB, showing areas of cyanosis interspersed with paler areas where blood-flow appears to be absent. It is unlikely that VOB occurs in man to anything like the same extent as is seen in animal species, but it is of interest that during hypotensive anaesthesia the surface of the liver in man may look cyanotic or show a rather waxy appearance.

Apart from the effects of hypotension itself, LBF may be altered directly by the effects of anaesthetic agents on splanchnic blood-flow (SBF) (Cooperman, 1972). Halothane has little effect on SBF other than a reduction due to the decrease in arterial pressure seen with this anaesthetic. Indeed, halothane may protect against the constricting effects of circulating catecholamines or hypercarbia (Epstein et al., 1961). In contrast, cyclopropane increases systemic arterial pressure, but causes a 33% decrease in LBF, as a result of its sympathomimetic effects on the splanchnic circulation; ganglion blocking drugs abolish this action and restore splanchnic blood-flow to normal (Price et al., 1965). Similarly, methoxyflurane causes a decrease in LBF but, in this instance, the effect is stated to be primarily on the hepatic artery (Libonati et al., 1973). In the isolated perfused canine liver, methoxyflurane increases hepatic arterial pressure through a direct effect on the hepatic artery. Libo-
nati and her colleagues (1973) showed that when a coeliac artery angiogram was performed under methoxyflurane anaesthesia, there was little or no flow via the hepatic artery. The mechanism of this effect is unknown. Methoxyflurane, like halothane, may decrease systemic arterial pressure when administered in high concentrations. The effects on the hepatic artery, however, occur at relatively low concentrations; therefore measurement of systemic pressure during methoxyflurane anaesthesia may be misleading with respect to LBF.

The use of spinal and extradural anaesthesia to induce hypotension leads to splanchnic vasodilatation and a decrease in perfusion pressure of the liver (Larson et al., 1974). A high spinal or extradural anaesthetic (with or without the addition of adrenaline) leads to a decrease in LBF of some 25%, which is comparable to that seen during halothane or cyclopropane anaesthesia.

In the normal unanaesthetized state the centrilobular liver cell, being most distal from the blood supply to the liver, exists in a situation where its oxygen supply is always rather precarious. It is clear that any of the changes mentioned above, particularly systemic hypotension, may compromise the centrilobular cells with respect to their oxygen supply and could therefore lead to damage. In practice, evidence of such damage is difficult to obtain. Price and his colleagues (1966), measuring hepatic venous Po₂ and the production of excess lactate by the liver, were unable to show that there was any evidence of hepatic hypoxia in healthy individuals undergoing anaesthesia. It is not clear, however, whether the combination of certain anaesthetics (e.g. methoxyflurane) with deliberate hypotension, perhaps in the presence of pre-existing liver damage (which may not necessarily be detectable by standard liver function tests or indeed have been looked for before operation), may lead to liver cell damage. A study of changes in liver function during hypotensive anaesthesia would be of interest, but as yet no such study has been carried out.

It is now common practice to use an infusion of sodium nitroprusside to induce hypotension. Initially, this technique proved extremely successful, and there were few records of any complications. Recently, several cases have been described where there was apparent "resistance" to nitroprusside, manifest as an inability to produce hypotension despite large doses, in combination with an increasing metabolic acidosis (Macrae and Owen, 1974; Jack, 1974). The aetiology of this resistance is not clear. However, it is of interest that this description also fits the syndrome of idiopathic lactic acidosis. In this condition, patients, who are often undiagnosed diabetics or have liver disease, develop an increasing metabolic acidosis with no evidence of circulatory insufficiency. It is known that once arterial pH decreases below 7.1, the enzyme systems in the liver responsible for the conversion of lactate to bicarbonate no longer function adequately. In this situation not only is the liver unable to metabolize lactate, but it is suggested that it switches over to active production. Could it be that, in some circumstances, sodium nitroprusside interferes with the enzyme system responsible for lactate metabolism as well as B₁₂ metabolism (Vessey et al., 1974), thus initiating lactic acidosis?

THE KIDNEY

Renal blood flow (RBF) is controlled in two ways, as a result of extrinsic autonomic and hormonal regulation, and by intrinsic autoregulation.

When small or moderate amounts of the catecholamines, adrenaline and noradrenaline, are present in the circulation there is an increase in systemic arterial pressure accompanied by a decrease in total RBF, but glomerular filtration rate (GFR) is unchanged. When non-physiological doses of catecholamines are administered, particularly when infused intravenously, they may produce very large decreases both in RBF and GFR. The extent of the changes is also governed by the existing cardiovascular state, and low plasma sodium or high plasma potassium concentrations or a deficiency of corticosteroids may decrease the vascular response (De Wardener, 1973).

In addition to the effects of either exogenous or endogenous catecholamines, the renin-angiotensin system is relevant when considering RBF. Although a decrease in RBF will initiate renin release from the juxtaglomerular cells of the afferent arterioles, sodium balance as detected by the macula densa is probably more important (Tobias, 1962). An α-globulin in plasma converts renin to angiotensin I, which is converted to angiotensin II, a potent pressor and renal vasoconstricting substance. Many factors are responsible for activating the renin-angiotensin system, and in addition angiotensin II controls the release of aldosterone. The effects of angiotensin are similar to those seen following adrenaline infusions; thus, small amounts reduce
RBF without affecting GFR, but increasing quantities decrease both RBF and GFR. Scornik and Paladini (1964) showed that reduction in RBF seen during haemorrhagic hypotension was the result of increased concentrations of circulating angiotensin, in addition to increases in catecholamines. The balancing factors against the renin-angiotensin system are probably some of the prostaglandins. When prostaglandins are infused there is an increased blood-flow to the outer nephrons, which have short loops of Henlé, resulting in a diuresis and loss of sodium; whereas the increased blood-flow to the juxtaglomerular nephrons, with their long loops of Henlé, results in sodium retention. How prostaglandins play their role in the control of intrarenal blood-flow and the regulation of water and sodium balance is not clear.

Antidiuretic hormone (ADH) secretion is stimulated by morphine and probably by most of the inhalational agents, and therefore oliguria is common during anaesthesia. Urine flow, therefore, may not be related to either RBF or GFR in this situation.

The oxygen consumption of the kidney is 8–10 ml/min/100 g tissue, and is related to RBF, which is highest in the cortex and lowest in the medulla (1–2% of total RBF). Hypoxia to a Po2 of 50 mm Hg has no effect on RBF, but hypercapnia evokes a sympathetic response leading to a decrease in RBF (De Wardener, 1973). This also occurs during anaesthesia, and therefore PaCO2 should be measured when RBF is studied.

Miles, Venton and De Wardener (1954) showed that there was autoregulation of RBF over a range of changes in mean arterial pressure of 80–180 mm Hg. This autoregulation occurs within the kidney itself, since it is also seen in the denervated perfused isolated organ. GFR is also autoregulated, and it has been suggested that there are cells which are sensitive to changes in perfusion pressure, located in the capillaries close to the glomerulus. Autoregulation of RBF is abolished during general anaesthesia and decreased RBF occurs with even moderate decreases in arterial pressure (systolic value of 80–90 mm Hg; Larson et al., 1974). If arterial pressure decreases below these values, renal blood-flow may decrease to the point where urine flow stops. It is well recognized that acute renal failure may then ensue, but the mechanism is not clear. It is believed that increased renin-angiotensin activity initiated by the decrease in RBF is responsible for the changes seen in acute renal failure. Supporting evidence is the fact that renal biopsies taken early in acute renal failure rarely show any changes in glomerular structure.

As with the brain, there is obviously some critical value of RBF below which acute renal failure may occur. This probably varies from individual to individual, it may be related to pre-existing renal damage, and it is a combination of the various extrinsic and intrinsic factors which may affect the kidney during anaesthesia. Since autoregulation is said to be abolished by all anaesthetic techniques, RBF is dependent primarily on changes in arterial pressure and the presence or absence of circulating catecholamines. Provided, therefore, that induced hypotension does not reduce RBF below the critical value for the kidney, it is unlikely that serious renal damage will ensue. Since GFR is also not autoregulated during anaesthesia, monitoring of urine output may be a useful parameter when considered in conjunction with the arterial pressure.

Prevention of acute renal failure following surgery, by adrenergic blockade, has not been successful. Mannitol, however, although not preventing anoxic damage, may prevent blockage of the tubules by casts or compression caused by intestinal oedema. It has been used successfully to prevent the acute renal failure associated with aortic aneurysm surgery, where the kidneys are often rendered ischaemic (Luck and Irvine, 1965).

**THE HEART**

Blood-flow through the coronary circulation is mainly dependent on myocardial metabolic demands (Merin, 1973) which are determined by cardiac rate, systolic arterial pressure and the velocity of contraction of the ventricle (Rowe, 1974). The coronary circulation demonstrates autoregulation, altering its vascular resistance by myocardial metabolic demands in the face of changes in perfusion pressure. Ganglion blocking drugs, by reducing arterial pressure and cardiac work, lead to a decrease in cardiac output, coronary blood-flow and left ventricular oxygen consumption. Since coronary blood-flow is mainly dependent on mean aortic pressure, there is obviously a limit to the hypotension which is tolerable. Depression of myocardial contractility is seen during deep halothane anaesthesia (Prys-Roberts et al., 1974) and, under some circumstances, after administration of ganglion blocking agents or β-adrenergic blockers.

Arterial PCO2 may affect cardiac output and thereby coronary blood-flow. Changes in PCO2 between 20 and 40 mm Hg primarily affect the
cerebral circulation, but from 40 to 55 mm Hg there is an increase in cardiac output (which can be blocked by β-adrenergic blockers). Thereafter, up to Pco\(_2\) 70 mm Hg, there is myocardial depression which is age-related (Eckenhoff et al., 1974).

The healthy heart will tolerate marked decreases in perfusion pressure, and even in disease seems remarkably tolerant, as may be seen in open-heart surgery. However, it would seem sensible to be cautious with induced hypotension in patients with coronary artery disease, and particularly if hypotension is combined with hypocarbia and direct depression of myocardial contractility (Prys-Roberts et al., 1974).

REFERENCES


