HYPOXIC BRAIN DAMAGE

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Irreversible hypoxic or ischaemic brain damage is the most important potential hazard to any patient subjected to general anaesthesia, and in the context of the present brief review the terms hypoxic and ischaemic can be taken as synonymous since the basic abnormality is the same, namely an inadequate supply of oxygen to neurones. The primary disturbance may vary widely: for example, respiratory or cardiac arrest, cardiac dysrhythmia or an episode of hypotension; but the vital factor with regard to the ultimate clinical outcome is whether or not satisfactory resuscitation can be achieved before the occurrence of irreversible brain damage. Fortunately complications of this type are rare, but there is little or no information available about the incidence of hypoxic brain damage in so-called "anaesthetic deaths", although failure to return to the preoperative conscious level must be indicative of some degree of brain damage. Reasons for this lack of information are not difficult to find, the principal one being that the brains from fatal cases are rarely subjected to detailed neuropathological analysis. Furthermore, autopsies on "anaesthetic deaths" are usually undertaken under warrant by forensic pathologists and the unfixed brain is summarily sliced in the postmortem room when it is impossible to recognize recent hypoxic brain damage, including frank cerebral infarction, macroscopically. When the brain has been properly dissected after adequate fixation, an infarct of about 18-24 hr duration may just be recognizable, but even an experienced neuropathologist may fail to identify extensive neuronal necrosis if it is of less than 48-72 hr duration (fig. 1). It is only by the microscopical examination of numerous large representative sections of brain that recent hypoxic brain damage can be identified with certainty and its distribution analysed.

Thus, published reports of cases of established hypoxic brain damage occurring in the course of general anaesthesia or in the immediate postanaesthetic period have tended to be rather haphazard. In most of the reported cases, too, there is a dearth of critical physiological data about the patient's cardiovascular status at the time of the catastrophe, since the immediate priority is resuscitation rather than the recording of arterial pressure, heart rate, blood gases, etc. There is therefore very little information available as to the smallest hypoxic insult that is likely to produce brain damage, or from how severe an insult a patient is likely to make a reasonable recovery. In the context of true circulatory arrest at normal body temperature, however, complete clinical recovery is unlikely if the period of arrest is more than about 5-7 min (Brierley, 1972).

Neurones are the cells in the body most sensitive to hypoxia since they have an obligative aerobic glycolytic metabolism, and consciousness is lost within a few seconds of complete oxygen deprivation. Their supply of oxygen depends on the cerebral blood flow (CBF) and the oxygen content of the blood. The CBF in turn depends on the cerebral perfusion pressure (CPP), namely the difference between the mean systemic arterial pressure (SAP) and the cerebral venous blood pressure.

TYPES OF BRAIN HYPOXIA

These have been classified by Brierley (1972) as follows:

1. Stagnant,
   a. Ischaemic, due to local or generalized arrest of CBF.
   b. Oligaemic, due to local or generalized reduction in CBF.
2. Hypoxic, due to a reduced oxygen content of the inspired air leading to hypoxaemia.
3. Histotoxic, due to poisoning of neuronal oxidative enzymes.
4. Hypoglycaemic, due to a deficiency of the substrate glucose.

The histotoxic and hypoglycaemic types are not relevant to a consideration of hypoxic brain damage associated with general anaesthesia.

Stagnant hypoxia.

Hypoxic brain damage due to stagnant hypoxia may occur in association with true circulatory
arrest or an episode of hypotension. The first of these is usually recognized almost at once and immediate remedial action is taken. Adequate cerebral perfusion, however, does not necessarily recommence as soon as a heart rate and arterial pressure are recordable, and a poor postarrest circulatory state may be as important as the duration of complete arrest in the pathogenesis of brain damage (Miller and Myers, 1972). It is only on this basis that irreversible brain damage, after an arrest which has apparently lasted for only 1 or 2 min, can be explained.

Systemic hypotension sufficiently severe to produce brain damage is much more difficult to recognize and to define, particularly since it is well known that the human brain can tolerate quite a low arterial pressure for a considerable time as in hypotensive anaesthesia. The physiology of cerebral blood flow has been reviewed by Harper (1965), but the salient factors will be summarized here. The preservation of CBF when SAP is low is brought about by autoregulation which can be defined as “the maintenance of a relatively constant blood flow in the face of changes in perfusion pressure” (Harper, 1972). As the SAP falls, the cerebrovascular resistance also falls because of autoregulatory dilatation of cerebral arterioles, with the result that CBF remains within normal limits over a wide range of SAP. There is no general agreement as to the principal factor responsible for this vasodilatation; it may be mediated by pressure sensitive smooth muscle elements in arteriolar walls or by metabolic factors such as a fall in tissue Po$_2$ and tissue pH, or an increase of tissue Pco$_2$. When cerebral vasodilatation is maximal, the cerebrovascular resistance cannot fall further; the CBF is then linearly related to the CPP. In the presence of normal autoregulation, the critical level of SAP is about 50 mm Hg (Harper, 1972).

The cerebral arterioles also respond to alterations in the blood gases when SAP is within normal limits; an increase in Pa$_{CO_2}$ or a decrease in Pa$_{O_2}$ produces arteriolar vasodilatation and hence a fall in cerebrovascular resistance. Thus, if arteriolar vasodilatation as a result of hypercapnia or hypoxia...
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in chronic hypoxic or hypercapnic states, as in chronic respiratory insufficiency, and probably also in some patients with occlusive arterial disease in the carotid and vertebral arterial systems, there may thus be some vasodilatation of cerebral arterioles even when SAP is normal. Such patients are particularly vulnerable to a fall in SAP since potential autoregulatory preservation of CBF is reduced. Autoregulation will also be impaired if a patient is hypoxaemic in the postanaesthetic period. Finally, autoregulation appears to be lost in a wide range of acute conditions producing brain damage—acute head injuries, haemorrhagic and ischaemic strokes, and a previous episode of hypoxia (Bruce et al., 1973). The last of these could be an important factor if a patient under general anaesthesia experiences more than one episode of cardiovascular collapse. Thus, there are many circumstances in which cerebral autoregulation may be impaired prior to an episode of hypotension. The level of CPP at which brain damage is produced in man is not known, but in primates with a normal PaO₂, brain damage does not appear to occur until the CPP falls to less than 25 mm Hg (Brierley et al., 1969).

Hypoxic hypoxia.

A fall in the oxygen content of the blood, of sufficient severity to produce irreversible brain damage, is unlikely to occur in the course of general anaesthesia except in the context of some technical fault. Even in such circumstances, oligaeamic factors are probably again of considerable importance. Thus, in primates subjected to severe hypoxic hypoxia in the decompression chamber, the severity of the hypoxia required to produce brain damage will also produce myocardial depression and a reduction in cardiac output (Brierley and Nicholson, 1969). It is likely, therefore, that the principal importance of some degree of hypoxic hypoxia in the context of general anaesthesia is that it produces cerebral arteriolar vasodilatation which, in turn, renders the brain more susceptible to a fall in SAP, and to oligaeamic hypoxic brain damage.

NEUROPATHOLOGY

Various patterns of hypoxic brain damage occur (Adams, 1967; Brierley, 1972), but because of the frequent lack of precise information as to a patient's cardiovascular status at the time of the episode, there is inevitably still some speculation as to the precise nature of the haemodynamic disturbances which produce these patterns. Nevertheless, by analysing the distribution of brain damage in a particular case, the neuropathologist can reconstruct with a fair degree of accuracy the disturbances in CBF responsible for its occurrence. The brain damage may be diffuse, that is the lesions are poorly delineated, or focal (Adams, 1967), but there is also considerable variation in the intensity of the damage in the affected areas, this being related to the different vulnerabilities of the constituents of the nervous system to hypoxia. The mildest structural damage is selective neuronal necrosis, but this may still be associated with evidence of severe brain dysfunction if the necrosis is widespread. If the hypoxia is more severe, neuroglial cells are also affected and frank cerebral infarction occurs. In the most severe lesions there is necrosis of blood vessel walls in addition and, in such circumstances, the infarct will be haemorrhagic if CBF becomes re-established through the necrotic tissue. The various patterns are also affected by the selective vulnerability of certain neurones to hypoxia, namely those in the hippocampus (Ammon's horn), in the third, fifth and sixth layers of the cerebral cortex, in certain parts of the basal nuclei, and in the Purkinje cells in the cerebellum.

The microscopic analysis of recent hypoxic neuronal damage of only a few hours' duration in man may be hindered by the inevitable presence of varying degrees of autolytic change in the brain. The earliest clearly identifiable abnormality is classical ischaemic cell change; the neurone is shrunken and its triangular shape intensified, its nucleus is pyknotic, and its cytoplasm takes on abnormal staining properties. A definite diagnosis of cell death is greatly enhanced by the presence of incrustations (small, relatively dense bodies lying on or close to the cell surface) as these cannot be confused with even advanced autolytic changes (fig. 2). The next stage is homogenizing cell change when the cytoplasm becomes progressively paler and homogeneous and the nucleus smaller (fig. 3). If the patient survives for more than 24–36 hr, the neuropathologist's task is made much easier because of more advanced abnormalities in neurones and the appearance of early reactive changes. With the passage of a few days, the dead neurones

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disappear, reactive gliosis becomes more intense, and obvious disintegration of tissue becomes apparent macroscopically (fig. 9). If the patient survives for more than a few weeks, the affected tissue becomes shrunken, intensely gliosed and sometimes cystic (figs. 4 and 5).

Ischaemic hypoxic brain damage (cardiac arrest).

There is characteristically diffuse neuronal necrosis in the cerebral cortex which tends to increase in severity from the frontal and temporal poles to the occipital poles. The necrosis may be total (fig. 6) or it may be restricted to the third, fifth and sixth cortical layers (fig. 7). It tends to be more severe within sulci than on their crests. The hippocampus is particularly vulnerable, especially the Sommer sector (fig. 8). This selective necrosis may occasionally be identifiable macroscopically if the patient survives for more than a few days (fig. 9). Neuronal necrosis is also common in the amygdaloid nuclei. The pattern of damage in the
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basal nuclei is less constant, but tends to be most common and severe in the caudate nucleus and in the adjacent part of the putamen. In the thalamus the anterior, dorsomedial and ventrolateral nuclei are the most susceptible but, in contrast to the structures already mentioned, hypoxic damage is usually restricted to selective neuronal necrosis, frank infarction being uncommon. In the cerebellum, there is characteristically diffuse necrosis of Purkinje cells. Damage to the brain stem nuclei tends to be more severe in infants and young children than in adults.

Patients with severe diffuse brain damage due to cardiac arrest rarely survive for more than a few days (Bell and Hodgson, 1974), but occasionally they may remain alive in a persistent vegetative state for longer periods (Brierley et al., 1971; Jennett and Plum, 1972; figs. 4 and 5).

Oligaemic hypoxic brain damage.

This occurs characteristically in association with an episode of systemic hypotension. Three main patterns have been defined (Adams et al., 1966). (1) In the first type, ischaemic damage is concentrated in the boundary zones between the main cerebral and cerebellar arterial territories (fig. 10). If the lesions are large and of a few days' duration, they can be easily identified with the naked eye (figs. 11 and 12). Microscopic examination is required, however, to determine their precise position and size, while recent lesions can only be identified thus. They vary in size from sharply defined irregular areas of necrosis in the cortex through total necrosis of the cortex, to a large wedge extending from the cortex almost to the angle of the lateral ventricle (figs. 13–15). They tend to be particularly large in the parieto-occipital regions where the territories of the anterior, middle and posterior cerebral arteries meet, and they are characteristically bilateral if they are due to an episode of systemic hypotension. There is variable involvement of the basal nuclei, particularly of the head of the caudate nucleus and the upper third of the putamen. This is the boundary zone between Heubner's branch of the anterior cerebral artery and the lenticulostriate branches of the middle cerebral artery. The hippocampus is usually not involved.

On the basis of clinical evidence (Adams et al., 1966; Adams, 1974), and experimental studies on primates (Brierley et al., 1969), this type of brain damage appears to be caused by a major and
Fig. 8 (A) Normal left hippocampus (Ammon's horn). (B) Selective neuronal necrosis in left hippocampus, particularly in the Sommer sector, i.e. its lateral (left) convexity.
Cresyl violet. Horizontal bar represents 1 mm.

This type of damage appears to be associated with hypotension of relatively slow onset but of long duration. Autoregulation allows an even distribution of the available CBF, but the supply of oxygen is inadequate.

(3) In the third type, there is again generalized damage in the brain, but there is a marked accentuation of ischaemic damage in arterial boundary zones. This appears to be associated with the abrupt onset of hypotension, which is responsible for the accentuation of damage in boundary zones, followed by a sustained period of less severe hypotension which causes the more diffuse damage.

The least common of these patterns is the second type, and it differs from stagnant hypoxic brain damage by reason of the relative preservation of the hippocampus. In the two commoner types the cortical damage, in contrast to ischaemic hypoxic brain damage, is focal and is accentuated in boundary zones, and there is again relative sparing of the hippocampus. If brain damage is particularly severe, however, the hippocampus may be involved (Brierley et al., 1969; Adams, 1974). Many examples of the first type have now been described (Brierley, 1972; Adams, 1974) and in all of them there has been a known episode of hypotension, or good clinical grounds for suspecting that the patient had experienced at least a transient episode of hypotension.
Hypoxic brain damage

This can occur theoretically when severe hypoxaemia is produced by obstruction of the respiratory passages, by hypoventilation, from the inhalation of inert gases, or exposure to high altitude as in decompression aviation accidents. Brain damage can be produced in primates by pure hypoxic hypoxia brought about by atmospheric decompression (Brierley, 1972), but the pattern is indistinguishable from that produced by severe hypotension with normal arterial oxygenation; the pattern is very similar to the third type of oligaemic hypoxic damage referred to above. Brierley suggests, therefore, that hypoxic hypoxia can produce brain damage only through the medium of secondary hypoxic depression of the myocardium; that is, there must be an oligaemic component.

DISCUSSION

There seems little point in attempting a comprehensive review of previously recorded cases of hypoxic brain damage associated with general
anaesthesia, in view of the lack of detailed information about the clinical and neuropathological findings. The first well-documented report is probably that of Wolf and Siris (1937), who reported four patients who were operated on in the sitting position. In each case there was infarction in the boundary zones between the anterior and middle cerebral arterial territories, but the significance of ischaemic damage in these zones was not appreciated at that time. The importance of head-up tilt

has been long recognized (Brierley and Cooper, 1962; Eckenhoff et al., 1963), and according to Bourne (1973) the evidence incriminating the traditional upright or semi-upright position of the patient as the most important factor contributing to death in dental anaesthesia continues to accumulate. Head-up tilt, however, is not an essential factor in the production of severe oligemic hypoxic brain damage.

There are other situations where ischaemic brain damage is particularly prone to occur in the course of surgical operations. In open heart surgery a reduced CBF, and air embolism, seem to be the principal factors involved (Brierley, 1967). According to Stockard, Bickford and Schauble (1973), extracorporeal perfusion at pressures below 50 mm Hg can result in ischaemic brain damage, the risk of this complication being roughly proportional to the depth and duration of the hypotension. The extent of atheroma of the cerebral arteries, and the age of the patient, also appear to be of significance. There has been considerable interest recently in the fall in SAP associated with the use of methylmethacrylate bone cement in orthopaedic operations (Powell et al., 1970; Adams et al., 1972). These are usually patients in the older age groups who are more likely to have pre-existing occlusive arterial disease of the carotid and vertebral arterial systems. Indeed, brief episodes of cardiac dysrhythmia (heart block, ventricular tachycardia or atrial fibrillation) may produce transient ischaemic
attacks in the older age group (McAllen and Marshall, 1973). Severe ischaemic brain damage can occur, however, as a result of a short-lived episode of circulatory arrest or severe hypotension in the young adult with no evidence of occlusive arterial disease.

What, then, are the implications of this brief review of hypoxic brain damage to the anaesthetist? Episodes of total circulatory or respiratory arrest will be recognized and appropriate remedial measures instituted immediately. The majority of patients who suffer such arrests either experience such profound brain damage that they live for only a very short time, or they make an uneventful recovery. On the basis of published reports and personal experience, it would appear to the writer a very short time, or they make an uneventful recovery. On the basis of published reports and personal experience, it would appear to the writer that a more insidious danger in the course of general anaesthesia or in the postanaesthetic period is an unrecognized episode of hypotension, or one that is recognized without its possible implications being appreciated, since there is a wide range of circumstances in which cerebral autoregulation may be impaired. It is not uncommon to find small ischaemic lesions in arterial boundary zones in patients who in the past have been subjected to major surgery; although this does not establish the association, instances of severe oligaemic hypoxic brain damage which cannot be due to anything other than a severe hypotensive episode are occasionally encountered in cases of “anaesthetic deaths”, although none has been recorded. I suspect, therefore, that if true respiratory or cardiac arrest are excluded, the greatest danger to the patient under general anaesthesia could be a reduction in CBF due to inadequate CPP, the manifestations of which may range from postoperative coma or severe dementia, with a poor prognosis, to only transient neurological or psychiatric dysfunction.

**SUMMARY**

The principal causes of hypoxic brain damage in relation to general anaesthesia are defined. The haemodynamic disturbances which reduce the oxygen supply to the brain are reviewed briefly, and the various patterns of brain damage so produced are described. While recognizing the importance of respiratory or cardiac arrest, it is suggested that an episode of hypotension is a more insidious danger in the course of general anaesthesia or in the postanaesthetic period. This danger is increased if there is any impairment of cerebral autoregulation.

**REFERENCES**


