TREATMENT OF ARTERIAL OCCLUSION UNDER OXYGEN AT TWO-ATMOSPHERES PRESSURE*

BY

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This lecture on the treatment of arterial occlusion deals with some of the experimental studies and clinical observations we have made in this field using the experimental pressure chamber recently installed at the Western Infirmary, Glasgow.

The term "arterial occlusion" covers a multitude of disorders, common, disabling, dangerous. It includes injuries to the main vessel of limb, arterial embolisms, and all the chronic obliterative diseases affecting the cerebral, coronary, and mesenteric vessels as well as those of the lower limb. Occlusion of these different arteries gives rise to clinical effects of quite diverse character which come to the notice of physicians, surgeons, and various groups of specialists. But fundamentally it is a single disease, exerting its effect in a single way, by the sudden or gradual interruption of the blood supply to a part.

Such ischaemia has two primary effects. On the one hand it reduces the oxygen supply to a part, and on the other hand it leads to retention within the part of carbon dioxide and other products of tissue metabolism. It is beyond our power to modify greatly the retention of toxic products, but the lack of oxygen can be compensated very simply and by a method which has been well understood for over a century. Our own contribution which I report here has been merely to apply this old-established knowledge and to make it available for the treatment of our patients.

Physiology of Oxygen Transport

Let me first remind you of the physiological conditions under which oxygen is transported in the blood in normal circumstances (Fig. 1). By far the greater part of the oxygen is carried in the red blood cells combined as oxyhaemoglobin. In a patient with a

normal haemoglobin level, breathing air at normal atmospheric pressure, arterial blood contains about 19.5 vols. of oxyhaemoglobin per 100 ml. of blood. At this level the haemoglobin is about 95% saturated, so there is very little scope for improvement.

Oxygen is also carried in the blood in simple physical solution in the plasma. Under normal conditions only a very small amount

is carried in this way—approximately 0.25 vol. %—but this is of special importance because as a physical solution its level can be raised very simply by increasing the ambient pressure. In the case of the human subject it is necessary to place the patient in a pressure chamber and administer oxygen by a face-mask or intratracheal catheter. When this is done, if the pressure within the chamber is raised to 2 atmospheres (absolute), the amount of oxygen in solution in the plasma is raised from 0.25 to 4.2 vols. %—that is to say, more than 16 times the normal level.

The total effect of this is to raise the oxygen content of the blood from rather less than 20 vols. % almost up to 25 vols. %—a quite considerable increase. However, in addition to this there is a further potential benefit, for by increasing the tension of oxygen in the blood-stream the rate of oxygen diffusion into underperfused and anoxic tissues is enhanced. Let me remind you that, while the red cells act as floating storehouses of oxygen, the rate at which oxygen will diffuse from the blood, through the capillary wall to the tissue fluids and to the fixed cells of the part, depends upon the gradient of partial pressures between the plasma and the tissue cells.

Experimental Ligation of Coronary Artery

Some years ago we decided to attempt to obtain experimental evidence to determine if the theoretical benefits to be obtained in this way would be of clinical value in conditions in which the blood supply of a part is interrupted. For this purpose it was necessary to choose an experimental situation in which ligation of a particular blood-vessel could be relied upon consistently to give measurable effects. It was necessary also that the situation should be one in which the comparatively small increase in the oxygen, such as might be obtained in a pressure chamber, might be sufficient to modify that effect.

Mr. George Smith, Reader in Surgical Cardiology in the University of Glasgow, on the basis of his own previous experience, suggested that the coronary circulation might provide such an experimental situation, and with Dr. D. D. Lawson he agreed to put the matter to the test.

Mr. Smith's previous work and that of others had shown that, in dogs, if a ligature is applied to the circumflex branch of the left coronary artery (Fig. 2) the blood supply of more than a third part of the myocardial muscle mass is interrupted and that in most cases this is sufficient to produce ventricular fibrillation and death

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FIG. 1.—Mode of transportation of oxygen in the blood in normal circumstances.

within the hour (Fig. 3). This result is obtained consistently in about 60 to 70% of cases. In the remaining 30 to 40% of cases the collateral circulation is sufficient to avert death, at any rate for the experimental period. It has been shown, moreover, that the critical level of

FIG. 2.—Dog's heart showing point of ligation of the left circumflex coronary artery. The muscle supplied by this branch has been injected with indian ink. Reproduced by permission of the *British Journal of Surgery*.

FIG. 3.—Outline representation of Fig. 2. Reproduced by permission of the *British Journal of Surgery*.

hours; death was due in nearly all cases to ventricular fibrillation, which made its appearance within 15 to 30 minutes of the start of the experiment.

In the case of the remaining 10 dogs, immediately after the artery had been ligated the animal was placed inside a makeshift pressure chamber constructed from a hospital autoclave (Fig. 4) and oxygen was introduced from a cylinder until a pressure of two atmospheres was attained. In this group the result was quite striking. All of the dogs showed on the electrocardiograph tracing some evidence of ischaemic changes, but only one of the dogs died within the experimental period of two hours. From these results, which were later confirmed in a larger series of 50 dogs, it was clear that the small increase in dissolved oxygen, reaching the ischaemic muscle either through coronary collateral circulation or directly from the interior of the heart, had been sufficient to achieve this notable result.

blood supply is a very narrow one, so it seemed possible that the comparatively small increase in oxygen content to be obtained by pressurization might be sufficient to have a measurable difference in the results.

This proved to be the case. Smith and Lawson carried out the standard procedure of ligation of the left coronary in 30 dogs, of which 20 were used as controls. In 10 of the dogs after the vessel had been ligated the animal was kept in room air at normal atmospheric pressure. In the other 10 control dogs oxygen was applied by an intra-tracheal catheter, but the pressure was maintained at one atmosphere. In each of these groups 6 of the 10 dogs died within the experimental period of two

The success of this experiment gave us encouragement to go on to further observations, both in animals and in the human subject. We were encouraged further by Boerema's (1956) report on his own pressure chamber. At this time support was gained from the Advisory Committee for Medical Research in Scotland, and on their recommendation a grant of £10,000 was obtained

FIG. 4.—Showing use of the pressure chamber.

from the Department of Health in Scotland to construct a pressure chamber for experimental work and also for clinical observations. The chamber was installed in June, 1960, and has since been in active use for a variety of purposes.

The experimental chamber, which is made of welded steel, is a horizontal cylinder 18 ft. (5.5 m.) long by 11 ft. 6 in. (3.5 m.) in diameter, comprising a main chamber 14 ft. (4.3 m.) in length and a small air-lock. The pressure is raised by a motor compressor, and an ingenious system of valves ensures a copious exchange of air. The temperature is under thermostatic control.

The chamber is designed to work at two atmospheres (absolute). This pressure was chosen partly for engineering considerations and partly because it seemed sufficient to provide a considerable increase in the level of oxygen in solution in the plasma, without the risk of complications which have been reported to develop occasionally at higher pressures. The chamber itself contains air. Within the chamber the patient breathes oxygen administered by a face-mask. There were therefore two possible complications to be considered—namely, the risk to the attendants of nitrogen bubbling (caisson disease) on decompression, and the risk to the patients of poisoning by prolonged administration of oxygen.

At two atmospheres the risk of nitrogen bubbling is known to be very small, and the maximum rate at which the chamber is decompressed under normal circumstances leaves a large safety margin.

The risk of oxygen-poisoning is also small at the comparatively low pressure of two atmospheres. Moreover, in this respect there is probably an important difference between 100% oxygenation, such as is observed in experimental animals within a sealed oxygen chamber, and the subtotal oxygenation obtained by means of a face-mask. At any rate, up to date we have obtained no evidence of oxygen-poisoning, though several patients have been maintained in the chamber for 48 hours and one patient for over 80 hours.

Clinical Observations

Since the chamber was installed 18 months ago it has been in use for a large number of clinical observations on various conditions characterized by local or general tissue anoxia. Our experience with carbon-monoxide poisoning has been reported elsewhere (Smith and Sharp, 1960; Lawson, McAllister, and Smith, 1961).

Among the arterial disorders, with which this lecture is mainly concerned, we have made observations in cases of injury to the main blood vessels of a limb and in cases of chronic obliterative disease complicated by pain or by threatened or actual gangrene. On the experimental side we have made observations related to obstruction of the cerebral vessels and also related to total circulatory arrest.

Injury to the Main Artery of a Limb

In a young patient with an injury to the main artery of a limb there is a good expectation that if the immediate danger of gangrene can be averted a collateral circulation will develop sufficient to maintain the vitality of the part.

The most notable case we have treated in this category was that of a boy aged 16 who sustained a compound fracture-dislocation at the ankle as a result of a motor-cycle accident (Smith, Stevens, Griffiths, and Ledingham, 1961). The anterior and posterior tibial vessels and the peroneal vessels were divided and the foot remained attached to the leg only by the tendons and their sheaths and two strips of skin only 4 cm. across. A mid-leg amputation seemed inevitable. However, my colleague Mr. Smith decided to try to preserve the foot. The cut ends of the torn posterior tibial artery were joined by suture and the dislocation was reduced. No reconstruction of the veins seemed possible and venous blood leaked from the wound for the first two days.

The patient was treated in the pressure chamber almost continuously for 48 hours and intermittently for the succeeding three days. After the first three hours in the chamber the foot became pink in colour and it remained so subsequently except during brief intervals when the compression was lowered, when the toes became cyanotic. Eventually the toes became gangrenous, but the rest of the foot remained viable so that it was possible eventually to perform a mid-tarsal amputation.

Another case in this category came under treatment more recently. A man aged 26, under treatment for dislocation of the ankle with wide separation of tibia and fibula, developed signs indicating compression of the anterior and posterior tibial compartments of the leg, with absence of pulses, stocking anaesthesia of the foot, and greyish cyanotic discoloration of the forefoot. Those in charge had no doubt that under ordinary treatment there would be a strong probability that the foot would require to be amputated. He was placed in the chamber and remained there continuously for over 80 hours, with occasional brief periods of decompression. The colour of the foot rapidly returned to normal and the area of anaesthesia gradually diminished. At the time of writing it is certain that the whole foot will remain viable. A further interesting feature here is that the pain, which was considerable, was relieved soon after treatment in the chamber, but it returned during the brief periods of decompression.

Peripheral Vascular Disease

We have made a clinical trial of a large number of patients with chronic obliterative disease of the vessels of the lower extremity. These patients go into the chamber in groups of four or five and stay there for two to three hours daily for up to 15 days.

In this type of case it is difficult to obtain objective evidence of the effect of treatment, and indeed in view of the gross organic vascular changes the possibility of recognizable improvement is remote. However, we have some evidence of improvement in a group of patients with severe ischaemic pain. There were 11 patients in this group, suffering from atherosclerosis or thromboangiitis obliterans with severe rest-pain which had failed to respond to other methods of treatment, including, in some cases, prolonged stay in hospital. In most of these patients the pain was severe enough to prevent sleep. During the period of treatment care was taken that apart from the daily period in the pressure chamber no other change was made in their regimen.

Nine patients in this group claimed to gain relief from the pain. In some cases the relief occurred quite dramatically while the patient was in the chamber, only to return to its former intensity during the intervals of treatment. In others the relief was more lasting. In all of these cases objective evidence of relief was seen in the reduced need for sedatives.

It is fully recognized that there are fallacies in interpreting subjective improvement, and undoubtedly in a new and dramatic form of treatment the influence of suggestion should not be discounted. However, old men with arteriosclerosis are not, as a rule, suggestible subjects and our patients certainly had been proof against all previous attempts to convince them of benefit.

Thromboangiitis Obliterans

We have had two patients with thromboangiitis obliterans who appeared to have benefited by treatment in the pressure chamber. The first was a man aged 29 with a six-year history of vascular disease. The great toe had been amputated two years previously, but the wound had broken down three months ago, leaving a painful ulcer. In his case treatment in the chamber for several hours daily over a period of three weeks was followed by rapid healing of the ulcer.

The second man was admitted with moist gangrene of the great toe and extensive oedema of the foot and leg due to secondary infection. In his case treatment in the chamber was combined with the administration of antibiotics with considerable improvement over three and a half weeks, so that it was possible to perform a limited amputation of the forefoot. In these two cases, also, the evidence falls short of what is scientifically desirable. Much further experience will be required for the final assessment.

Cerebral Vascular Occlusion

My colleagues have made experimental observations on cerebral vascular occlusion in the dog, as a preliminary to clinical applications in cerebral vascular disease and in cases where temporary interruption of the cerebral blood flow is required during operations on vascular lesions within the skull.

The method adopted has been to occlude both carotid and both vertebral arteries low in the neck. In the dog this does not interrupt the whole blood-flow to the brain,

for collateral routes exist through multiple small arterial channels in the heavy muscles of the neck. As a rule this collateral circulation is insufficient in itself, but our observations show that it is enough to maintain life under conditions of increased oxygenation in the pressure chamber.

The technical data relating to these experiments have been published elsewhere (Smith, Lawson, Renfrew, Ledingham, and Sharp, 1961). The method is to apply removable clamps to the four arteries. Electrocardiograph tracings are made and an electroencephalographic record is obtained using silver electrodes inserted through burr-holes in the skull.

In five dogs this procedure was carried out first of all at normal atmospheric pressure, then the clamps were released and the process was repeated under full oxygenation at two-atmospheres pressure. Finally the chamber was decompressed and the process repeated for a third time at normal pressure. One of the dogs was found subsequently to have an anomalous circulation sufficient to maintain a copious blood-flow despite the fourfold ligatures. It showed no adverse effects throughout. In the remaining four dogs, when the vessels were occluded initially at normal pressure signs of cerebral anoxia developed very rapidly. The electroencephalographic record showed deterioration within 15 seconds and there was a complete loss of cortical rhythm within one minute (Fig. 5). By contrast, when the clamps were reapplied under full oxygenation at two-atmospheres pressure, apart from transient slowing of the rhythm in one dog, the electroencephalographic record remained entirely normal throughout the experi-

FIG. 5.—E.E.G. record after arterial occlusion. Reproduced, by permission, from *Surgery, Gynecology, and Obstetrics*, 1961, 113, 13.

FIG. 6.—Record of mean femoral artery blood-pressure in the dog during carotid and vertebral artery clamping. Reproduced, by permission, from *Surgery, Gynecology, and Obstetrics*, 1961, 113, 13.

mental period of about 30 minutes. It was clear that the additional oxygen had been sufficient to prevent severe cerebral anoxia. The blood-pressure changes are shown in Fig. 6.

The third phase of this experiment, in which the clamps were reapplied after the pressure had been reduced to normal, gave an unexpected and interesting result, for here only one of the dogs showed some disturbance of the electroencephalographic tracing, and this was quite transient. This phase was repeated in a further series of four dogs, with similar results.

To investigate this result more closely, in two further dogs the experiment was repeated and samples of arterial blood and blood from the internal jugular vein were withdrawn for oxygen estimation. As is indicated in the Table the arteriovenous difference in oxygen content was 9.7 volumes at the start of the experiment. After the clamps had been in position for five minutes, under full oxygenation at two-atmospheres pressure, the arteriovenous difference was raised to 18.9 vols. %.

Blood Oxygen Levels (Vols. %)

	Pre-occlusion	Post-occlusion	
		5 mins.	30 mins.
Femoral artery	23	23	23
Jugular vein	13.3	4.1	10.4
Difference	9.7	18.9	12.6

as was to be expected in view of the greatly reduced blood-flow through the brain and the consequently greater extraction of oxygen from the blood. However, samples removed 30 minutes later showed that the arteriovenous difference had fallen to 12.6 vols. %, indicating that during this period the flow rate through the brain had greatly increased. It was clear that treatment in the chamber, by preventing the initial cerebral anoxia, had enabled the animals to survive long enough for an adequate collateral circulation to open up.

These experimental observations have clinical implications in relation to cerebral disease and in relation to operations on the brain. It is clear that in conditions in which the blood supply to the brain—or to a particular portion of the brain—is reduced to a critical level the small increase in oxygenation produced in the pressure chamber might be sufficient to prevent anoxic damage.

Such conditions include atherosclerosis of the internal carotid and cerebral arteries with stuttering hemiplegia, homonymous hemianopia due to cerebral thrombosis, and retinal-artery occlusion. As regards operations on the brain, it is thought that to operate within the chamber may prove advantageous in conditions such as intracranial angioma and aneurysm of the internal cerebral artery, when it is desired to occlude both carotid arteries for a prolonged period.

Total Circulatory Arrest

It seemed possible that if the tissues were overloaded with oxygen by full oxygenation in the chamber at two-atmospheres pressure it would be possible to withstand total circulatory arrest for a longer period than normal, and that if pressurization were combined with moderate hypothermia the resulting safe period of cardiac arrest might be sufficient to permit open heart operations.

The method has been applied to dogs under full oxygenation at two-atmospheres pressure. The hypothermia has been induced by surface cooling until the mid-oesophageal temperature reaches $27^{\circ} \pm 1^{\circ}$ C., and

then to produce total arrest by clamping the superior and inferior venae cavae, the aorta, and the pulmonary artery. At the end of the agreed period the clamps are released, the wound is closed, and the animal's progress is watched. In successive experiments the period of arrest has been lengthened. It will be seen that in the control dogs (hypothermia at one-atmosphere pressure of oxygen) the maximum safe period of cardiac arrest is about 20 minutes. Up to that point there has been no difficulty in getting the heart restarted, and the dogs have survived permanently with no neurological or other sequels. Of the five dogs in which cardiac arrest at normal pressure was maintained for 25 minutes, two could not be restored at the end of this period, and one other dog developed slight ataxia which persisted for two days. By contrast, in the dogs treated in the

chamber at two-atmospheres pressure a period of arrest of 30 minutes was well tolerated and one dog survived even as long as 40 minutes.

At the present time further experiments are in progress to determine the minimum circulatory flow rate necessary to raise the period of cardiac arrest to one hour or more. It is hoped that in this way it may be possible to simplify the technique of artificial circulation in open heart surgery.

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PREVENTION OF VIRUS DISEASES IN THE COMMUNITY*

BY

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The control of infectious diseases depends mainly on the production of immunity by vaccines, and on epidemiological control—with the identification, quarantine, and treatment of infected individuals. The balance between the usefulness of these two methods—vaccination and epidemic control—varies from a disease like typhoid, where (in the United Kingdom) we rely exclusively on epidemic control, to a disease like poliomyelitis, where, at least for the next few years, we shall have to rely largely on immunization.

One of the great heresies about immunization is that epidemics of a particular disease will cease when about 75% of children have been immunized against it. It has been said, for example, that "For adequate protection of the population against epidemic spread of smallpox, at least 75% of infants should be vaccinated" (Ministry of Health, 1956). This is not true, for in the past extensive outbreaks of smallpox occurred in Britain at a time when there was at least 75% acceptance of infant vaccination, and in many places 75% of the susceptible population have been naturally immunized by infections of smallpox, poliomyelitis, and other viruses and yet outbreaks of these diseases occurred and continued to occur.

Risks Associated with Smallpox Vaccination

In any immunization programme we must be quite sure that the risks associated with immunization are less than the risks of contracting the disease. I would like to consider this in relation to smallpox vaccination, the main risks of which are generalized vaccinia and post-vaccinal encephalitis. How common are these? How often are they fatal? *Unfortunately it is impossible to obtain accurate data on this.*

The available figures (Table I), which are not very reliable, give the mortality from primary vaccination in England, Wales, Scotland, and part of Northern Ireland for the period 1951 to 1958.

It seems probable that deaths from vaccination are often not reported; there is no obligation to do so and,

furthermore, some doctors may not report that vaccination has injured or killed a baby if he has persuaded the parent to accept it, and if he has always thought that vaccination was a safe procedure. It is our duty to measure the danger of vaccination, but unfortunately, and perhaps we all share some blame, this has not been carefully done. Can we do anything about this?

TABLE I.—Mortality Per Million Primary Vaccinations—England and Wales, Scotland, and Part of Northern Ireland (1951–8) (Griffith, 1962)

Complications	Age-group, Years			
	<1	1–4	5–14	15+
Generalized vaccinia ..	4.7	0	0	0
Post-vaccinal encephalitis ..	9.0	0	0	5.3
Others	1.7	1.9	0	0
Total ..	15.4	1.9	0	5.3

It is often suggested that vaccination is best done in infancy because it will prevent complications when revaccination is carried out in later life for travel or military service. The published figures (Table II) show that the total mortality from primary vaccination in infancy plus revaccination at 15+ is 18.4 per million compared with 5.3 if primary vaccination is done in

TABLE II.—Complications and Mortality Per Million of Primary Infant Vaccination Plus Revaccination at 15 Years and Over, Compared with Primary Vaccination at 15 Years and Over (Dixon, 1962). Data from England and Wales, Scotland, and Part of Northern Ireland (1951–8)

Complications	Primary Vaccination in Infancy plus Revaccination at 15+		Primary Vaccination at 15+	
	Complications	Mortality	Complications	Mortality
Generalized vaccinia ..	58.8	4.7	76.9	0
Post-vaccinal encephalitis ..	22.4	11.0	26.3	5.3
Others	?	2.7	?	0
Total ..		18.4		5.3

adult life—a highly significant difference. The presumed diminution of risk to an individual vaccinated in infancy and revaccinated as an adult—which was one of the pillars on which our policy was founded—can be seen to be fallacious. It is also often said that infant

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