INTRA-ARTERIAL OXYGEN IN PERIPHERAL VASCULAR DISEASE

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The injection of small quantities of oxygen or of various other gases into the brachial artery of the normal subject is followed by marked vasodilatation in the hand and forearm which persists for an hour or more (Duff, Greenfield, and Whelan, 1953). This observation suggested a possible application in the treatment of patients with ischaemic disorders of the limbs. Much of the disability in these patients is a direct consequence of reduced blood flow to skin and muscle, and it was felt that if vasodilatation could be obtained comparable in degree and duration to that in normal people symptomatic benefit might result. Intra-arterial oxygen has been employed as a mode of therapy in ischaemic disorders of the lower limbs by Lemaire, Loeper, and Housset (1948); they were impressed with its effect in improving symptoms. Since then several workers in Germany (Wernitz and Dörken, 1954; M. Ratschow, personal communication, 1955; Hasse, Köble, and Linker, 1955) have claimed therapeutic benefit from intra-arterial oxygen therapy.

This paper presents the results of a detailed study of circulatory changes induced by intra-arterial oxygen injections in patients with peripheral arterial disease involving upper and lower limbs. The changes are compared with those following intra-arterial injection of three potent vasodilator drugs: tolazoline ("prisco"), hydrallazine ("apresoline"), and phenyl-iso-butyl-n-p-hydroxy ephedrine ("dilatal").

Methods

The investigations were carried out at a room temperature of 20–24° C. The patient rested on a couch for at least an hour before observations were made. In the case of the upper limb, injections were made into the brachial artery in the antecubital fossa; for the lower limb, they were made into the femoral artery in the groin. The limb into which the injection was made was raised slightly. A continuous infusion of 0.9% saline was maintained into the artery from a mechanically driven syringe, and the gaseous oxygen was added slowly to the stream of saline through a side-arm in the connecting tubing.

On most occasions measurements of blood flow were made by the technique of venous occlusion plethysmography (Barcroft and Edholm, 1943). The segment of limb being investigated was enclosed in a water-filled mechanically stirred plethysmograph (Greenfield, 1954), the water temperature being 31–32° C. for the hand and foot, and 34–35° C. for the forearm and calf. Normally the corresponding segment of the opposite limb was used for control observations, but on a few occasions on which it was desired to record simultaneously from the calf and the foot of the limb which received the injection no control observations were made. The venous collecting pressure was usually 50–70 mm. Hg, but at the peak of vasodilatation in the foot it was sometimes necessary to employ pressures as low as 30 mm. Hg. Cuffs at the ankle and wrist respectively were

inflated to a pressure of 200 mm. Hg for one minute before and during the recording of calf and forearm blood flows. After each injection of oxygen or of a vasodilator drug, blood flow records were taken at frequent intervals for one and a half to three hours. If at the end of this time the blood flow was still significantly raised further observations were made at intervals until it had returned to the resting level.

On some occasions changes in the skin temperature of the foot following injection were measured by a thermo-electric junction.

The dose of oxygen was 10 ml. for the upper limb and 30 ml. for the lower limb, given over a period of 10 to 15 minutes. In the case of the vasodilator drugs the quantities injected intra-arterially approached or equalled the full intravenous doses, so that a very high local concentration was attained in the limb injected. For the lower limb the quantities were: tolazoline 50 mg., hydrallazine 20 mg., dilatal 10 mg.; for the forearm and hand the corresponding quantities were 25–40 mg., 10–12 mg., and 5 mg. The vasodilator drugs were administered steadily over 5 to 10 minutes.

Eighteen patients were studied, as shown in Table I:

TABLE I

Disorder	Male	Female	Total Cases	Under 50 Years	Over 50 Years
Raynaud's phenomenon ..	3	2	5	3	2
Intermittent claudication ..	8	2	10	4	6
Ischaemic necrosis of feet ..	2	1	3	0	3
Total	13	5	18	7	11

Appearances

Following injection of tolazoline the skin of the limb distal to the site of arterial puncture rapidly became bright red; this persisted for about an hour, then slowly faded. Colour changes subsequent to injection of hydrallazine and dilatal were similar but less pronounced.

The sequence of colour changes in the upper limb (Duff *et al.*, 1953) and lower limb (Hasse *et al.*, 1955) of healthy subjects following intra-arterial injections of oxygen has already been described. Similar changes were noted in the diseased limbs of the present study. As the slow infusion of oxygen began blanched patches appeared in the skin distal to the site of injection. A crepitant sensation was imparted to the palpating finger by the passage of minute emboli through the radial and posterior tibial arteries; tinkling sounds were audible on auscultation over these vessels, and sometimes they could be heard by the naked ear up to 10 cm. distant from the vessel.

The patient was often conscious of a prickling sensation in the limb along the course of the major vessels, but real discomfort was rare. Five minutes later the limb was uniformly of a waxy white hue, the distal pulses were of poor volume, and the superficial veins were collapsed. Soon, however, the characteristic blue and then red patches appeared on the skin, spread concentrically, and coalesced to give a marbled appearance. Next the blue patches faded and the limb was uniformly erythematous. Colour changes were often noted in the ipsilateral lower abdominal wall and external genitalia owing to dispersal of gaseous emboli or vasodilator drug in the superficial hypogastric and external pudendal vessels. Localization of injected dilator drugs was sometimes seen, as evidenced by flushing confined to distinct areas, usually of the lateral or medial aspect of the thigh. Such localization was not seen after injection of oxygen, presumably because turbulence created by the fine stream of bubbles favoured more even mixing with the blood.

That the injected oxygen was distributed not only to the skin of the limb but also to the underlying muscle was demonstrated by measurement of the oxygen saturation of blood samples taken from a deep vein (draining muscle) and

a superficial vein (draining skin) before and after an injection of 5 ml. of oxygen into the brachial artery. Oxygen saturation was measured by a spectrophotometric technique (Roddie, Shepherd, and Whelan, 1956). Before the injection the oxygen saturation of the muscle blood was 55% and of the skin blood 69%. After injection the saturation of the blood from both sources rose simultaneously to attain values of 89 and 91% respectively within 25 minutes. Similar results were obtained in two other experiments, and indicate that the injection of gas into the brachial artery causes a dilatation of the vessels of both the skin and the muscle of the forearm.

Circulatory Changes in the Upper Limb

A typical series of results are shown in Fig. 1. This patient, a man of 64, suffered from severe Raynaud's phenomenon associated with arteriosclerosis; in addition he had worked with vibrating tools for a number of years.

FIG. 1.—Comparison of effects of oxygen, hydrallazine, tolazoline, and dilatal intra-arterially on hand blood flow of patient with Raynaud's phenomenon. Arrows indicate the times at which infusions of oxygen or vasodilator drugs began. Dots— injected side. Circles—control side.

During a period of three weeks seven oxygen injections were given, the results of which are summarized in Table II. It is seen that the duration of vasodilator response is variable. After the fourth and seventh injections the vasodilatation was no more prolonged than that obtained by tolazoline and dilatal. Similar results were obtained in the other patients with Raynaud's phenomenon.

TABLE II

No. of Injection	Hand Blood Flow (ml./100 ml./min.)			Approximate Duration of Vasodilatation (Hours)
	(i) Left Hand Before Injection	(ii) Left Hand at Peak of Vasodilatation	(iii) Right Control Hand Simultaneous with (ii)	
1	3.3	9.2	3.8	48
2	5.4	13.9	4.9	60
3	4.5	13.5	6.0	24
4	5.9	15.5	6.5	2.4
5	4.9	18.0	5.3	42
6	6.0	15.9	6.1	24
7	5.0	11.0	5.6	2.4

Circulatory Changes in the Lower Limb

Changes in calf blood flow following intrafemoral injection of oxygen and the three vasodilator drugs are illustrated in Fig. 2. The patient, a man of 37 with Buerger's disease, had suffered for two years from severe intermittent claudication; bilateral lumbar sympathectomy had produced only transient improvement and his

exercise tolerance was limited to 50 yards. Dilatal, tolazoline, and hydrallazine produced moderate increases in blood flow, with a return to the resting level in a few hours. In contrast, vasodilatation following intra-arterial oxygen persisted for over 30 hours.

Before the administration of oxygen this patient could make only 30 contractions of the calf muscles at intervals of two seconds against resistance; during the subsequent vasodilatation he was able to perform 80 similar contractions before the onset of severe cramp (Fig. 3). This suggests that the ability to perform work was improved by the injections; however, too much emphasis cannot be laid on this finding, since it is difficult to assess the role of psychological factors in the performance of such tests in intermittent claudication, and a precise measurement of work capacity (Shepherd, 1950) was not made.

FIG. 2.—Comparison of effects of oxygen, hydrallazine, tolazoline, and dilatal on calf blood flow of patient with severe intermittent claudication. Conventions as in Fig. 1.

FIG. 3.—Effect of vasodilatation induced by intra-arterial oxygen on onset of intermittent claudication. Vertical lines in upper frame indicate number of contractions of calf muscles carried out at 30 per minute before claudication forced patient to stop. Other conventions as in Fig. 1.

FIG. 4.—Vasodilator effect of intra-arterial oxygen on calf blood flow of a recently sympathectomized limb. Conventions as in Fig. 1.

Similar results were obtained in other cases of intermittent claudication in which studies of blood flow were made. While oxygen usually caused vasodilatation lasting 24 to 60 hours, on some occasions it was effective for only four to six hours. The response of the peripheral circulation was comparable in patients who had been subjected to lumbar sympathectomy to those in whom no operative procedure had been carried out (Fig. 4).

In two patients there was an unexpected fall in foot blood flow following injections of the vasodilator drugs. This was investigated by recording blood flows simultaneously from

FIG. 5.—Effect of intra-arterial oxygen, tolazoline, and hydralazine on foot and calf blood flow measured simultaneously in same limb of patient with severe intermittent claudication.

the calf and the foot of the injected limb; the results in one of the patients, a woman aged 50 with severe intermittent claudication, are shown in Fig. 5. It is seen that, following injection of both oxygen and vasodilator drugs, the foot blood flow falls simultaneously with a rise in calf blood flow. This variety of response was unusual; in most cases both foot and calf blood flows increased as illustrated by the observations (Fig. 6) on a young woman with acrocyanosis and Raynaud's phenomenon.

FIG. 6.—Effect of intra-arterial oxygen on calf and foot blood flow measured simultaneously in patient with acrocyanosis and Raynaud's phenomenon.

In the cases of ischaemic necrosis of the feet circulatory changes were assessed by recording skin temperatures at various sites on the feet and toes. A typical result is shown in Fig. 7. This patient, a man of 58, suffered from hypertension and arteriosclerosis with intermittent claudication and early gangrenous changes in the second toe of the left foot. During the two hours following the injection a gradual rise occurred in skin temperature recorded on the dorsum of the foot (from 22 to 28° C.) and the great toe (from 20 to 26.5° C.), the temperature on the control side remaining steady at about 23° C. At the end of four hours the skin temperature of the

great toe was gradually falling, but that of the dorsum of the foot remained at 28° C. More prolonged observations were not practicable, since the length of time which the patient could be kept in the laboratory was limited and the skin temperature of the control side varied widely with changes in environment. A small number of patients were treated with six injections of oxygen at weekly intervals. After individual injections the patients often claimed marked symptomatic improvement for a period of about two days—that is, for approximately the duration of the significant elevation of blood flow; the hands or feet felt warmer and the distance walked before the onset of claudication pain was increased. One patient noted improved healing of ischaemic foot ulcers, and another experienced such relief from attacks of Raynaud's phenomenon that sympathectomy was postponed. In general, how-

ever, the effects were short-lived, and there was no striking improvement in symptoms at the end of a short course of treatment.

A series of injections at short intervals of time were given to two patients in attempts to obtain a sustained elevation of flow. In the case of the upper limb (Fig. 8 A) the responses

FIG. 7.—Skin temperature changes on toes and dorsum of foot following intra-arterial oxygen in patient with arteriosclerosis and early gangrene.

FIG. 8.—Attempts to maintain vasodilatation by repeating intra-arterial oxygen injections at intervals. (A) Hand blood flow in a patient with Raynaud's phenomenon. (B) Calf blood flow in a patient with intermittent claudication. Conventions as in Fig. 1.

to the oxygen injection were very variable and a sustained increase in hand flow was not obtained by four doses over a period of 120 hours. In the case of a lower limb three injections over the same period of time resulted in a sustained increase in calf flow which was at no time less than double the resting level of flow (Fig. 8 B).

Discussion

Since the report by Singer (1943) several groups of workers have administered vasodilator drugs by the intra-arterial route to patients with occlusive arterial disease. A wide range of drugs including acetylcholine, histamine, papaverine, "hydergine," hexamethonium, and tolazoline have been used by Edwards *et al.* (1952). These authors have been encouraged by improvement in a large percentage of their patients to use the method on an increasing scale; in some cases surgical intervention was rendered unnecessary, and benefit was obtained in others in whom symptoms had recurred following surgery. The duration of action of any of the pharmacological preparations at present available is, however, short, and it was felt that the ideal vasodilator substance would be one with a much more prolonged effect.

The increase in the blood flow after oxygen injections in the patients is comparable to that obtained in normal

subjects. Usually the vasodilatation lasted for 24 to 60 hours. This is far in excess of that produced by any of the three drugs tried in the same patients. Sometimes, however, the vasodilatation was less well sustained, the blood flow falling to the resting level in six hours or less. It is unlikely that localization of the injected gas to one branch of the main limb artery entirely explains this finding, as there was a generalized distribution of the initial colour changes in the skin of the injected limb on these occasions.

The administration of oxygen has been a relatively safe procedure. The injections are made with the patient horizontal, and the injected limb is held slightly raised to guard against the possibility of gas emboli spreading proximally against the current of arterial blood and causing visceral infarction. The possibility exists that, in patients with degenerative arterial disease, injections may cause local damage to the arterial wall or dislodge material from atheromatous plaques. Care is taken to make each injection at a different site and to use a sharp short-bevel needle, 1 mm. in external diameter, and no such complications have been encountered. Additional precautions include the use of smaller quantities of oxygen than those employed by the Continental authors, and administration at a much slower rate. Hasse *et al.* (1955) consider that injections should not be given to patients with recent acute thrombotic episodes, and that the method should be used with caution in patients with advanced ischaemic lesions in the feet, since in them the injected oxygen may be sufficient to occlude entirely the few patent vessels. The only complication in the present series occurred in such a case.

The patient, a man of 47, suffered from arteriosclerosis and Raynaud's phenomenon with ischaemic changes in the skin of the finger-tips. The resting hand blood flow, despite a warm environment (room temperature 22° C.; plethysmograph temperature 33° C.), was less than 1 ml./100 ml./minute; after injection the usual sequence of colour changes in the skin was noted, but no rise occurred in blood flow. Next morning the forearm was swollen and tender, and attempts to dorsiflex the wrist caused severe pain. The diagnosis was infarction of an extensor muscle. Gradual resolution occurred over the next four days, and there was no residual loss of power. In view of this experience, intra-arterial oxygen was not subsequently given to any case of peripheral vascular disease where the resting blood flow was excessively low, or where a dilator response had not been noted to occur during indirect heating or following the injection of tolazoline intra-arterially.

In two cases the foot blood flow was considerably reduced after intrafemoral injections of oxygen and also of the vasodilator drugs. This paradoxical finding is probably due to a "borrowing" phenomenon, all or most of the available blood in the lower limb being short-circuited through the dilated vessels of the thigh and calf. A similar phenomenon has been noted after lumbar sympathectomy in some patients with severe ischaemia of the feet (Freeman, Leeds, and Gardner, 1947). In such cases intra-arterial vasodilator substances of any variety are clearly contraindicated.

Clinical trials in France (Lemaire, Loeper, and Housset, 1948) and Germany (Ratschow, personal communication, 1955; Hasse *et al.*, 1955) appear to have established intra-arterial oxygen injections as a useful form of therapy in peripheral vascular disease. We hesitate to draw conclusions from our own cases, as our experience in this respect is limited and as the present investigation was designed to obtain objective information concerning the dilator effect of oxygen in patients with peripheral vascular disease rather than to assess its value as a therapeutic agent. However, the present results demonstrate that the vasodilatation induced by intra-arterial oxygen injections is much more prolonged than that following injections of potent vasodilator drugs. It is concluded that in those cases of peripheral vascular disease in which administration of vasodilator drugs by intra-arterial injection is indicated oxygen should be used in preference to other dilator substances.

Summary

The effects of intra-arterial injections of oxygen on the local circulation have been studied in 18 cases of peripheral vascular disease involving upper and lower limbs. In most cases the injections resulted in an increase in blood flow lasting for 24–60 hours. In the same patients injections of tolazoline, hydrallazine, and dilatal caused only relatively transient increases in blood flow.

Provided certain precautions are taken, the intra-arterial injection of oxygen is a safe procedure. It should not, however, be used in patients with very low resting blood flows or in those with recent occlusion of a major vessel.

Occasionally the paradoxical effect of reduction in blood flow through the foot may be observed to follow intrafemoral injection of oxygen, but this effect is also apt to occur with any other potent vasodilator substance.

It is concluded that oxygen should be used in preference to other vasodilators in the treatment of peripheral vascular disease by intra-arterial injections.

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PULMONARY TUBERCULOSIS IN NORTH GLASGOW

AN EPIDEMIOLOGICAL STUDY

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Greenwood, in his report to the Health Committee of the League of Nations on the relation of housing to tuberculosis in London, is quoted as stating: "Only by an exact study on a small scale can truth be reached. The massed data of official statistics are too complex to yield any decided answer" (McDougall, 1949).

With this statement in mind we have, during the past year, made a personal detailed investigation into the socio-economic state of nearly all the new significant cases of adult-type pulmonary tuberculosis in patients aged 14 years and upwards arising in the northern area of Glasgow. The 250,000 people in this area are mainly of the working class, and live in what we consider to be a representative sample of the whole of Glasgow in respect of new and old housing. A new case was