INTRAVENOUS OXYGEN * †

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HISTORY

NYSTEN (1, 2) in 1811, probably was the first person to inject oxygen into the blood stream of a living animal. He was able to inject 20 cc. of oxygen, repeating these injections every three to four minutes, administering a total dose of 100 to 150 cc. without harming the animal, a dog, but a dose of 200 cc., injecting 30 to 40 cc. every minute, was fatal. He stated, further, that two injections each of 20 cc. of nitrogen every two minutes would not kill the animal. He was the first to observe the characteristic liquid heart sounds and stated that all the blood became of an arterial color.

Demarquai (3) in 1866, stated that the venous blood did not become arterial, but that wound edges remained red and vascular. He concluded that intravenously administered oxygen remains at least partly fixed and is used for nonrespiratory purposes.

Gaertner (4), in 1902, was the first to suggest administration of oxygen intravenously in a continuous stream and was the first to recommend its use in man. He performed autopsies on dogs that died during these injections and said that he found bubbles in the right ventricle but never in the left. He concluded that the flow of blood containing oxygen bubbles does not obstruct the pulmonary circulation.

Mariani (5), in 1902, apparently was the first to administer oxygen to a living human being by the intravenous route. He injected 80 cc. in thirty minutes, then 40 cc. during the next fifteen minutes. The total dose was thus 120 cc.; the rate of injection was 160 cc. per hour; both values are fairly small. The patient, who was dying of tuberculosis, was apparently unharmed and was reported to have been helped by the procedure, but died the next day.

Stuertz (6), in 1904, published a report concerning intravenous oxygen. He administered large doses to dogs, up to one-third of their oxygen requirements. He recommended intermittent injections and suggested that the injections be made some distance from the heart. He warned of the danger of dilating the heart and advised watching

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pulse, respiration and heart sounds. He thought that pneumonia presented a contraindication to this procedure, since the right side of the heart, being already embarrassed, might further be injured. He concluded that intravenously injected oxygen was used for respiratory purposes.

In 1905, Neudoerfer (7) treated a man by this method; the patient was reported not to have been injured by the injection, but died some time afterward.

Tunnicliffe and Stebbing (2) reported their work in 1916. They had originally intended to oxygenate solutions to be administered intravenously and, after reviewing the literature, injected gaseous oxygen into the veins of 3 human beings, with good results. They gave the therapeutic dose as 10 cc. per minute and the toxic dose as 20 cc. per minute. They described the appearance after an overdose, which is simply giddiness, flaccidity and unconsciousness. They, too, stressed the danger of dilatation of the heart, but believed that the procedure was safe. They concluded that the effect of intravenous oxygen was greater than could be explained on the basis of merely relieving cyanosis.

Torraca (8), in 1922, applied this technic to the guinea pig. The oxygen was liberated into the peritoneal cavity, a curious finding, since oxygen is reported to be absorbed after injection into the peritoneal cavity (9).

Bourne and Smith (9), in 1927, rendered dogs hypoxic by lowering the oxygen content of their surrounding atmosphere before injecting oxygen, to evaluate the effect in hypoxic, rather than normal, animals, since patients who are to receive oxygen intravenously would be expected to be in a state of suboxygenation. They found that the hypoxemia was accentuated rather than dispelled, and attributed this to pulmonary embolism and right heart insufficiency. The animal dose was given as 1 to 2 cc. per kilogram per minute (but 0.75 cc. per kilogram, may, they warned, cause dyspnea); the human dose was 0.25 cc. per kilogram.

Alexandrescu-Dersca and Nanu-Mussel (10), in 1928, are reported to have performed this technic in man over one hundred times, but it is not clear that gaseous oxygen rather than an oxygenated solution was used.

Paunescu (10), writing in 1931, reported his work in dog and man. He maintained that he used a dry gas, but in the same article mentioned "saturated oxygen." He referred to Baiyeux's apparatus, and considered the procedure safe and beneficial.

Tsyganov (11), in 1934, published an account of his work on the dog using, probably for the first time, a water displacement apparatus. He encountered transient episodes of arrhythmia and tachypnea, but found no appreciable change in blood pressure, pulse or oxygen content of venous blood.

Dick (12), in 1939, working with dogs, found little good in the procedure. He believed that it resulted in a fall in blood pressure, a decrease in arterial blood oxygen, a rise in right ventricular pressure (which he considered to be an indication of pulmonary embolism), and an increase in depth of respiration (vagus reflex).

Singh and Shah (13), in 1940, described their application of this technic to the treatment of six persons suffering from severe pulmonary disease. Singh (14) had previously reported his experiences with this method in 1935. Their dose was 10 to 20 cc. per minute; they used alternating syringes and bubble counting. They believed, although their figures are not entirely convincing, that blood pressures and pulse rates showed uniform improvement, that reactions occurred occasionally and that oxygen embolism is not dangerous.

Ziegler (15), in 1941, described a new device for this purpose. From his own description of the apparatus and from my experiences with several models built according to Ziegler's specifications and with some containing slight modifications, his purpose does not seem entirely clear. A porous resistance block is inserted into the path of the oxygen; the gas is first dried, then passed through a wash bottle; a manometer is placed so as to show the difference between the pressures on the two sides of the water bottle. Ziegler stated that doses used by earlier investigators were too large, and attributed to this the reactions described by them. In addition, he advised using a narrow (22 gauge) needle. He believed that embolism occurred rarely, but warned of the necessity of watching pulse and respiratory rates, and mentioned several contraindications to this procedure.

Grodins, Ivy, and Adler (16) published their results in 1943. They reported hyoxemia, attributed by them to emboli, and rapid, shallow breathing.

In 1946 Jacobi (17) and his associates described the antishock properties of intravenously administered oxygen. They treated 3 patients, 2 of whom were greatly improved by this therapy. They noted increased blood pressure, slower respirations, better color and fall in hemoconcentration. They thought that embolism occurred rarely.

A report by Sanders and Isoe (18), appeared in 1947, describing their investigations in dog, man and *in vitro*. They could not detect an increase in blood oxygen, found that bubbles coalesced and did not dissolve, and found uniform adverse effects, including arterial hypoxemia, reactions (including spasm), tachypnea, and electrocardiographic changes (involving the T wave and ST segment). They maintained that embolism occurred commonly.

Weston and Karel (19), in 1947, concerned with what they believed to be the tendency of nitrogen to leave the blood and enter the oxygen bubbles and so increase their size, attempted to denitrogenate dogs before injecting oxygen into their veins. They encountered tachypnea and arterial hypoxemia and considered the method hazardous in the

anoxemic state, but it must be noted that their attempts lay in the direction of extrapulmonic oxygenation. While this may have been the original and obvious purpose of intravenous oxygen, I believe it is less important and less safely and consistently achieved than the dramatic effect of intravenous oxygen on shock, described by Jacobi and confirmed below.

Goodwin and Harmel (20), in 1949, paid considerable attention to the size of the oxygen bubble and, after experimenting with needles containing multiple perforations, used an ureteral catheter whose distal end was denuded of shellac and plugged, bubbles leaving through the finely woven fabric. They advised injecting far from the pulmonary bed into distant veins or arteries, and suggested that the animal's head be kept low during the injection to reduce the danger of formation of embolus. They stated that bubbles reaching the pulmonary bed cause tachypnea, and found arterial hypoxemia. They denitrogenated the dogs before injection, by offering them an atmosphere of pure oxygen, then apparently rendered several of them hypoxic by providing the animals with atmospheres deficient in oxygen. The nine articles appearing in foreign journals favor the procedure. The eleven articles published in American and English medical journals, referred to here, are evenly divided in their opinions.

PHYSIOLOGY

Nearly everyone who has viewed this form of therapy with enthusiasm has been well aware of the difference between air and oxygen in relation to the hazard of gaseous pulmonary embolism. Practically four-fifths of air is composed of nitrogen, whose introduction into the blood stream is neither beneficial nor safe. Oxygen, on the other hand, is physiologically valuable and is far more easily and safely contained in the blood. The incidence and hazard of air embolism must not be inflicted on a technic in which such a danger is markedly reduced and by means of which enormous benefit may be provided.

The amounts of oxygen injected are small. Assuming that the average individual inhales (exhalation is nearly the same, differing only slightly because of the respiratory quotient and carbon dioxide and water vapor content) 400 cc. at a time and breathes eighteen times each minute, he exchanges about 7500 cc. per minute. Of this, one-fifth, or 1500 cc., is oxygen. He consumes one-third, or 500 cc., of this amount (exhaled air contains 14 per cent oxygen). In my hands and in those of many investigators, 10 cc. per minute has been found to be an efficient and maximal dose; this is equivalent to 2 per cent of a patient's respiratory requirements. No appreciable decrease has been shown in the oxygen intake from inspired air when intravenous oxygen was offered.

Reported harmful results include the following not necessarily independent effects: (1) pulmonary embolism; its action is at least theo-

retically threefold: vascular spasm, reduction of the pulmonary bed and mechanical obstruction of the pulmonary circulation; (2) dilatation of the heart; (3) cardiac tampon, also called vapor lock, cardiac tamponade, or cardiac froth; (4) arterial hypoxemia, and (5) tachypnea. Some workers have reported deeper, some shallower, respirations. The outstanding objection to the use of intravenous oxygen has been the danger of pulmonary embolism. I have often heard liquid or gurgling heart sounds on the right side, but only once, when an overdose had been inadvertently administered, on the left side. Experiments *in vitro* demonstrating a lack of solubility of oxygen in blood cannot be considered directly applicable to this study, nor can the presence of oxygen bubbles along the course of a vein be viewed with great alarm, since it appears that complete solution takes place in the pulmonary circulation.

Beneficial aspects include the following: (1) the color is improved; (2) the blood pressure rises (note Jacobi's and the author's cases); (3) the pulse rate declines; (4) hemoconcentration falls; (5) blood vessels fill (a good sign of emerging from true shock); (6) respirations may be slowed, in some cases; (7) the mental state has been improved in some instances, and (8) pulmonary edema has been removed (15). Furthermore, this technic affords a method of introducing oxygen directly into the blood, by-passing the lungs, the apparatus required, aside from the difficulties of calibration, is simple, and the cost of administering oxygen intravenously is extremely small, about 10 cents per day, in contrast to an estimation of $6 to $20 for an oxygen tent (15).

The only contraindications suggested (15) up to this time are a marked diminution in the capacity of the vascular bed of the lungs, such as is found in emphysema and in advanced tuberculosis, and a marked dilatation of the right ventricle, shown by an unusually high venous pressure. These two conditions are often related since increased resistance to the flow of blood through the lungs is generally the cause of right ventricular dilatation.

APPARATUS

As the chief objection to this technic has been the danger of pulmonary embolism or cardiac tampon, the stumbling block in the path of the investigator has been the difficulty of maintaining a continuous, slow, constantly accurate flow of the gas. A machine used for this purpose must be easily regulated, calibrated and accurate, must provide a continuous flow and one that is independent of changes in the patient's venous pressure and, while gaseous oxygen is considered to be sterile, it must incorporate some means to provide sterility.

Many devices have been used for the intermittent or continuous intravenous injection of oxygen. They are as follows:

1. Single syringes.
2. Alternating syringes.
3. Bubble counting—as employed by Tunnicliffe and Stebbing (2), this included audiometer determinations.
4. Ziegler's apparatus (15).
5. Water displacement.

The apparatus which I use consists of a 4 liter inverted flask fitted with a four-hole rubber stopper. Tubing from each of these openings is connected individually to a regulated source of oxygen, to an open container of water (this is placed below the inverted flask and the tube is lowered just beneath the surface of the water), to an ordinary intravenous saline drip and to a narrow needle to be inserted into a vein. The flask is filled with saline solution or water and inverted after all tubes have been clamped. The tubes leading to the oxygen and to the open water are then opened, and the flow of oxygen from the cylinder is started. The oxygen displaces the liquid from the inverted flask into the open vessel below until the inverted flask is completely filled. At this point, oxygen should be allowed to escape into the lower container so that the inverted flask will be completely filled, and particularly to ensure maintaining the gas in the flask at atmospheric pressure. The tubes which had been open are closed and the other two are opened. The intravenous drip is slowly started at a previously determined rate. The saline solution displaces the oxygen from the flask and causes it to enter the patient's vein; each drop of saline displaces the equivalent of its volume of the gas, making possible the establishment of a very low rate of flow.

6. Thomas Oxinjector. This machine, although calibrated, is constructed for subcutaneous injection.

7. Bayeaux's apparatus (10).

8. Electronic. This device was shown to the author through the kindness of Dr. Jacobi and his associates at the Beth-El Hospital, Brooklyn, New York.

9. Pressure syringe. Many of the above devices are based on pressure calibrations rather than on true volume readings. In an attempt to avoid alterations in the rate of flow brought about by fluctuations in the patient's venous pressure, the following is suggested. A 10 cc. syringe is connected, by means of a cam joined to an explosion proof motor, electric or spring, to a two-way valve leading to a source of oxygen at atmospheric pressure and to the patient's vein. The motor is so regulated that the injection of 10 cc. takes a full minute; a clock spring should work well. The action of the cam then provides for rapid refilling of the syringe with oxygen. Such a mechanism is completely independent of venous pressure changes; it will neither be hurried nor slowed, but the plunger will move forward inexorably at the prescribed rate.

CLINICAL APPLICATION

Two cases are reported for evidence of the antishock properties of intravenously introduced oxygen.

Case 1.—An abdominoperineal resection of the large bowel was begun at 7:30 a.m. on an adult man in otherwise good condition, under endotracheal cyclopropane-curare anesthesia. At 11 a.m. the patient went into shock while the abdominal wall was being closed; blood was seen to flow from the urethra. Whole blood and plasma were administered intravenously into three of the patient's extremities. Vasopressor drugs were given subcutaneously and intravenously, with no effect. The patient was kept on the operating table and oxygen was administered continuously by inhalation. At 1 p.m. he was considered to have practically no arterial blood pressure; it could not be heard, there were no visible fluctuations of the dial and the pulse could not be felt anywhere. At 2:30 p.m., when he had been pulseless and without any ascertainable blood pressure for one and a half hours, all infusions of blood and plasma were discontinued and intravenous administration of oxygen was started. Within five minutes, a blood pressure of 90 mm. was plainly heard and the systolic pressure rose to 100 mm. in another minute or two. The surgeons were recalled, the incision was opened and about 4000 cc of blood was found in the peritoneal cavity. While the large bleeding vessels were being secured the patient died.

Case 2.—A young man was shot while attempting to steal an automobile. The .38 caliber bullet pierced the right lung, liver and left kidney. Bleeding was present during the latter part of the night and he soon went into profound shock; he was without ascertainable pulse or arterial blood pressure at 8 a.m.; blood and plasma were continued. Three hours later, at 11 a.m., oxygen was administered intravenously. A blood pressure of 90 mm. appeared in twelve minutes, 100 mm. in another two minutes. At this point a large dressing was removed from his wound (by an over-zealous intern), profuse bleeding ensued and the patient quickly died.

Neither patient survived, but the evidence of the antishock effect of intravenous administration of oxygen in the presence of gross hemorrhage is plain. Although the administration of whole blood and plasma in large amounts over a period of hours were without avail, intravenous oxygen restored the arterial blood pressure within minutes. It was thought by those who witnessed the injections that had the torn vessels been secured sooner in the one case and had the hemorrhage not been restarted in the other, very possibly both patients might have been saved.

The total doses used in these cases were only 50 and 120 cc. at the time that the arterial blood pressure was reestablished. In the absence of any elaborate apparatus, single or alternating syringes may prove satisfactory.

SUMMARY AND CONCLUSIONS

Intravenous oxygen was first intended to provide extra-pulmonic oxygenation, but this goal is not yet attainable. Small amounts of this gas, however, have remarkable antishock properties, and can be ad-

ministered with relative safety. Dangers of overdosage are far less to be feared in the presence of profound and intractable shock, in cases in which no treatment has offered hope and in which the prognosis is felt to be grave.

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