# INJECTIONS OF AIR AND OF CARBON DIOXIDE INTO A PULMONARY VEIN*

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It has been repeatedly demonstrated that the injection of air into a systemic vein leads to embolism of the smaller vessels in the lung and that such embolism is not apt to be harmful unless an extremely large volume of air is injected. When air is permitted to enter a pulmonary vein, on the contrary, relatively small amounts may cause death, since the air passes directly through the left heart to the systemic arteries. In this respect, the likelihood of cerebral or medullary embolism has received particular attention. Some chance observations in the laboratory, however, suggested to us that coronary embolism is the chief danger. Consequently, in a series of animals, we have injected air into a pulmonary vein in order to study the manner of death. Furthermore, as a companion study, we have compared the effects of air with those of carbon dioxide, with the possibility in mind that the latter gas might be relatively harmless in view of its solubility and of its property of entering into chemical combination in the blood.

*Method.*—The experiments were performed upon cats of varying size and age anesthetized by the intraperitoneal injection of sodium amytal. Artificial respiration was maintained through a tracheal cannula. The right and left fifth ribs were removed, the sternum was cut across, and the pericardium opened widely, so that the heart and lungs were clearly in view throughout the experiment. The air or other gas was injected directly into a pulmonary vein by means of an ordinary syringe and needle, a coating of oil preventing any escape of air about the plunger of the syringe. The speed of injection was limited only by the caliber of the needle, the injection requiring from one to six seconds depending upon the volume of air injected. Although most of the injections were made by way of the left superior vein, each of the other pulmonary veins was utilized at times without apparent variation in the result.

*Cause of Death.*—In each of 30 animals death was finally caused by injecting air into a pulmonary vein. In every instance it appeared that the death resulted from obstruction of the coronary arteries. After the air was injected into the vein, within a second or two one saw air bubbles descending the coronary arterial branches on the surface of the heart.‡ When the dose

* Submitted for publication July 5, 1939.

† Recipient of the Dr. J. B. Kass, Research Scholarship in Preventive Medicine.

‡ The uppermost part of the left auricle, *i.e.*, the auricular appendage, often served as an air-trap. After injection of a small dose of air it was sometimes necessary to express the air from this site before it would pass into the left ventricle and make its appearance in the coronary arteries.

was small, only a few tiny vessels near the apex became obstructed; they remained readily visible as branching white lines until solution or absorption of the air. This required from 5 to 20 minutes depending upon the amount of air which had lodged. When only a few such branches were obstructed, there was no visible disturbance of the beat or of the function of the heart.

With larger doses the air filled both coronary arterial trees, even including the main stems.* There it remained. At times a segment of blood interposed in the column of air would be seen to oscillate slightly with the beat of the heart, but there was never any progression of the column to suggest an escape through the capillaries. This complete obstruction of the coronary arteries led to a rapid ischemic failure of the ventricles. They became pale and dilated within two or three minutes. Various degrees of block were followed by ventricular fibrillation and death with the heart in extreme dilatation. This required five or six minutes after the injection. By this time the wink reflex was lost. The animal made violent agonal respiratory movements. A minute or so later the pupils had become extremely dilated and the animal appeared dead although the auricles maintained a regular beat for some minutes longer.

The manner of death, *i.e.*, the behavior of the heart, the appearance of the animal, and the time elements which pertained, were the same as when both coronary arteries are ligated (Moore and Greenberg,[6] 1937; Dennis and Moore,[2] 1938). This fact, together with the absence of convulsions and the occurrence of spontaneous agonal respiratory movements, led to the conclusion that death resulted primarily from coronary obstruction and not from embolism of medullary or cerebral vessels. The terminal cerebral asphyxia evidenced by the loss of reflexes, the dilatation of the pupils, and the agonal respirations was secondary to the failure of the heart.

In 29 of the 30 animals, death followed this cardiac pattern. There was no convulsion. In two of the animals, it was noted that the wink reflex was lost in one eye a minute sooner than in the other; however, in these

* In two animals injections of moderate doses of air repeatedly filled the right coronary artery while causing no embolism of the left artery. In two other animals the tendency was for the anterior descending branch of the left artery to become filled while the circumflex branch of the left artery and the right arterial tree received no air. In young animals with good arterial anastomoses the preservation of two of these three main arterial channels to the myocardium permitted the animal to survive. In spite of irregularities of rhythm and periods of partial dilatation of one ventricle the heart maintained its function. The disappearance of the air from the one vessel it filled required about 20 minutes. In the case of the right artery the air remained visible longest in a circular area about 1 cm. in diameter situated on the anterior surface of the heart just to the right of the interventricular sulcus and about one-third way up from the inferior cardiac border. In the case of the anterior descending artery the air tended to remain longest in a similar area on the right inferior aspect of the cardiac apex just to the left of the anastomotic connection between this vessel and the posterior descending ramus of the right coronary artery. Such areas were visible not only because the airfilled vessels appeared as branching white lines but also because the myocardium was dry, pale and gray in contrast to the moist, red appearance of the adjacent heart muscle.

animals there occurred spontaneous respiratory movements after the heart had ceased all coordinate activity, indicating that until that time the medullary centers were not paralyzed. Consequently, we are skeptical of the dangers of cerebral embolism while the horizontal position is maintained.

That the passage of air to the coronary arteries was independent of the animal's position was shown by Exper. 27, the one instance in which a convulsion did occur. In this experiment a sublethal dose of air was repeated—first with the animal board tilted to 30° head-down, then with the board tilted 30° head-up, and, finally, with the board horizontal. In the three positions, there occurred apparently identical amounts of coronary embolism, the air requiring in each instance about 15 minutes for absorption. Next the animal was given a lethal dose of air with the board horizontal, and, as it was dying with the ventricles fibrillating, convulsions occurred in the hind legs. We suppose these convulsions signified cerebral embolism although they occurred 34 minutes after the injection made with the head elevated. In three of the other experiments, injections were made with the animal board inverted so that the animal was suspended in a quadrupedal walking position. Death occurred from coronary obstruction just as when the animal was lying upon its back.

We do not infer that regardless of position all air injected by way of a pulmonary vein passes into the coronary arteries, but rather that, being the first aortic branches, the coronaries receive a considerable proportion of the air. In every animal we studied the coronary embolism of itself caused death, leading as it did to ventricular fibrillation.

*Fatal Dose of Air.*—Ordinarily, injections of volumes up to ¼ cc. per pound body weight were tolerated without sufficient disturbance of the heart to harm the animal. This dose would amount to 37.5 cc. of air into a pulmonary vein of a man of 150 lbs.* Doses exceeding ¼ cc. per lb. were apt to be fatal and doses exceeding ½ cc. per lb. were regularly fatal.

*Effects of Carbon Dioxide.*—In a number of animals we injected pure carbon dioxide into a pulmonary vein.† It appeared to be harmless. We made repeated injections, some as large as 3.0 cc. per lb. body weight, a quantity

* In six cats, we determined the ratio of heart weight to body weight. The figure ranged from 0.31 per cent to 0.55 per cent with an arithmetical average of 0.39 per cent. Smith[8] (1928) found that in man the normal heart averaged 0.43 per cent of body weight in the male and 0.40 per cent in the female.

† Samples were taken from a number of tanks of commercial carbon dioxide purporting to be pure. In every instance chemical analysis proved air to be present and injection of such a sample into a pulmonary vein resulted in coronary embolism in proportion to the amount of air in the mixture. Thereafter, we generated our own carbon dioxide by pouring concentrated hydrochloric acid over marble chips in a small glass flask. After the first violent bubbling had ceased the flask was closed with a one-hole rubber stopper carrying a glass tube. This tube was fitted with a rubber connection of a size to fit the nozzle of a Luer syringe. After a few minutes to permit all air to be displaced from the flask and tubing, the syringe was attached and the carbon dioxide allowed to flow into it by virtue of its own pressure, the plunger of the syringe being sealed with oil. With these precautions it was possible to obtain carbon dioxide practically free of air.

corresponding to 450 cc. for a 150 lb. man. In one animal we injected a dose of 2.0 cc. per lb. body weight three times in four minutes for a total dose of 6.0 cc. per lb. No lasting embolism resulted. Thirty minutes later the same animal suffered the typical coronary embolism death from an injection of one-sixth this volume of air.

During the injection of the carbon dioxide there was a loud "slap-slap-slap" sound—the "mill-wheel" murmur. The gas was seen to fill both coronary trees within a few seconds but in 15 to 20 seconds it was entirely replaced with blood. Even the tremendous doses employed caused too short a period of coronary obstruction to disturb the heart's rhythm. Although immediately after the injection the vessels were filled, within a few seconds a column of blood could be seen advancing down each artery. With every systole of the heart this column of blood advanced several millimeters. In eight or ten beats of the heart only a little of the gas remained visible. This remainder vanished in another few seconds except in instances when the gas was contaminated with air, in which cases a varying number of the smaller arterial branches remained visibly obstructed for some minutes.

*Discussion.*—In considering the dangers attending the entrance of air into the circulation one must distinguish between the systemic and the pulmonary veins. The fear that the accidental entrance of air into a systemic vein may result in sudden death has been dispelled to a great degree by the repeated demonstration that large volumes of air can be injected into the veins of animals without fatal results. In the dog from 3.5 cc. (Harkins and Harmon,[4] 1934) to 7.0 cc. (Wolffe and Robertson,[11] 1935) per lb. body weight is required to kill when given into the femoral vein in a single injection. Richardson, Coles and Hall[7] (1937) tried a method of continuous injection at a slow rate and in one dog injected 3,910 cc. over 87 hours' time before death occurred. Similar experimental results can be found as far back in the medical literature as one cares to go. In 1889, in a demonstration before the Philadelphia County Medical Society, Dr. H. A. Hare injected 60 cc. of air into the jugular vein of a 12-pound dog without harmful effect. In describing his experiments, Hare[3] wrote: "Magendie states that he has thrown, with all the force and celerity of which he was capable, 40 or 50 pints of air into the veins of a very old horse without his dying immediately, and Cormack (1837) blew the contents of his chest, twice filled, into the jugular vein of a horse before the animal exhibited any signs of uneasiness. Barthelmy has also found that in six horses, weakened greatly by the withdrawal of blood, as much as four to six liters of air must be introduced intravenously to cause death, and estimates, in consequence, that a man weighing 136 lbs. would be killed only by two-thirds of a liter." Hare concluded that "enormous amounts of air must enter a vein to cause death," and that "no such quantity can possibly find its way into a vein which has been injured with the knife of the surgeon."

Numerous studies have shown that air which enters a systemic vein is churned with the blood in the right ventricle to form a froth. Because of its compressibility this froth interferes to some extent with the expulsion of blood

from the ventricle. This phase, which is accompanied by a loud murmur, lasts but a few moments. The froth is ejected into the pulmonary artery and the bubbles of air lodge in the smaller vessels of the lung. Nitrogen is so sparingly soluble that the vessels remain obstructed for many minutes. Although massive doses of air may cause death in this manner, the pulmonary vascular bed is so capacious that large amounts are tolerated without sufficiently widespread obstruction to bring the lesser circulation to a stop. Furthermore, the pulmonary vessels are such an effective barrier that ordinarily none of the bubbles reach the left heart to lodge as emboli in the coronary or cerebral circulations.

In the case of a pulmonary vein, however, there is no capillary barrier to prevent the air reaching the left heart. As a result, small quantities, by lodging in certain medullary or coronary vessels, may cause cessation of respiration or failure of the heart. Van Allen, Hrdina and Clark[9] (1929) found that the dog's maximum tolerance for air injected into a pulmonary vein was only 1.5 cc. per Kg. body weight, whereas one dog survived an injection into the jugular vein of 76 cc. per Kg. In the experiments we have reported, the maximum by way of a pulmonary vein for the cat was 1.1 cc. per Kg. Van Allen, Hrdina and Clark stressed the principle of "air buoyancy." Because of the gravity factor the air tends to pass to the uppermost vessels. These workers found that with the animal in the dorsal, recumbent, horizontal posture the arch of the aorta is high and serves as a trap, as a result of which much of the air passes out the great arch branches to the head, neck, and upper extremities. With the head down little of the air passes to the fore part of the body but the coronary vessels are heavily involved.

In our experiments with cats little evidence of harmful cerebral embolism was encountered. On the contrary, regardless of the position of the animal, a fatal coronary embolism was the rule. Considering the position and configuration of the aortic sinuses it would be our judgment that the ventral recumbent position with the head down might result in the air passing by the coronary orifices without entering them. Except in occasional operations, however, this position would be impracticable. Moreover, in view of our experiments, we feel that there is little hope of lessening the dangers of air embolism by placing the patient in any special position.

To compare oxygen embolism with air embolism, Harkins and Harmon[4] (1934) calculated from the oxygen-unsaturation of venous blood that the minimum fatal dose of oxygen would be approximately 10 per cent greater than the minimum fatal dose of air. In a few animals in which we injected oxygen taken from commercial tanks which were labelled "pure," the gas appeared to produce just as lasting embolism as did air.

In this respect, the contrast between carbon dioxide and either air or oxygen was striking. Pure carbonic acid gas would not produce a lasting embolus. In explaining this difference one should bear in mind that carbon dioxide is an extremely soluble and highly reactive substance. We suppose that its solubility and its capacity as a weak acid to unite with the alkaline blood

buffers are the chief factors accounting for the rapid disappearance of gaseous carbon dioxide from the vessels. We do not believe that the gas escaped through the capillaries into the venules, for we never saw bubbles ascending the coronary veins. Furthermore, if one watched large bubbles of carbon dioxide gas in the middle of a column of blood, he saw them suddenly vanish as though they had dissolved in the blood.

The finding that pure carbon dioxide gas does not produce stable emboli when it is introduced into a vein, suggests several practical applications. It might well be substituted for air to provide the desired degree of collapse during closed intrapleural operations such as, for example, the endoscopic severing of pleural adhesions. While its absorption would probably be too rapid for use in therapeutic pneumothorax, it should be a very safe substance for the exploratory initial fill in a patient in whom pneumothorax is desired. Although the fact that carbon dioxide is much heavier than air suggests that it could be used in open thoracotomy, any admixture of the gas with air would lessen the protection from embolism. The authors have injected large amounts of carbon dioxide into the pleural cavity of the cat and know that the gas has been used without harm for pneumoperitoneum. However, since we have not injected it into the pleural cavity of man, we can make no recommendations in this regard other than to emphasize the necessity for the carbon dioxide to be pure if air effects are to be avoided.

We have been able to find only one previous report of the injection of carbon dioxide into veins. In 1924, Colle[1] reported that it produced embolism just as did air. We suspect that he was led astray through the use of ordinary commercial carbon dioxide, which, as we have noted, is often heavily contaminated with air.

In conclusion, it might be stated that the embolic effect of air requires an explanation. If blood passes through the smaller vessels, why cannot air? Apparently the lodging of air in the vessels centers about the fact that the air is present in bubbles having a resistant liquid film. Wilson and Ries[10] (1923) showed that with certain colloidal solutions the surface films of the foam behave as gel-like plastic solids rather than viscous liquids. As a result the superficial viscosity may be more than 1,000 times that of water. Such bubbles are extremely resistant to rupture. Similarly, Langmuir[5] (1938) has emphasized the viscosity and elasticity of certain protein films on water and believes that in such films the protein molecules actually undergo a form of "denaturation" to form a homogenous, continuous structure. It is our supposition that in air embolism the films of blood about the air bubbles have assumed to some degree this same rubber-like quality.

## SUMMARY

A considerable proportion of the air injected into a pulmonary vein of the cat lodged as emboli in the coronary arteries. This occurred regardless of the animal's position. In 30 consecutive experiments, the injection of a volume of air equalling or exceeding 0.5 cc. per lb. body weight caused a typical

coronary death. In only a few cases was there accompanying evidence of cerebral or medullary disturbance.

Upon injecting pure carbon dioxide into a pulmonary vein it was found that this gas would not produce a stable coronary embolus. Although an injection of 2 cc. per lb. body weight filled the coronary vessels, the gas was entirely taken up by the blood in 15 to 20 seconds and the heart was not visibly affected.

The appearance and behavior of the heart following injections of air and of carbon dioxide are described and the mechanism of air embolism is discussed. In relation to the absence of harmful effects from the intravenous injection of carbon dioxide certain practical applications are suggested.

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