GAS EMBOLISM: A COMPARATIVE STUDY OF AIR AND
CARBON DIOXIDE AS EMBOLIC AGENTS IN
THE SYSTEMIC VENOUS SYSTEM

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IN 1920 Rubin described a method of determining the patency of the
Fallopian tubes by the intrauterine insufflation of oxygen with the production
of an artificial pneumoperitoneum. Since that time, the principle of the Rubin
test for tubal patency has been universally accepted, although the technique
and apparatus originally described have undergone numerous modifications.
One of the earliest innovations was the substitution of carbon dioxide for
oxygen as the insufflating gas of choice, the reason being that it was more
rapidly absorbed from the peritoneal cavity, thus causing less postoperative
discomfort to the patient. Subsequently, occasional reports of gas
embolism with fatal results following the use of air or oxygen in diagnostic
Rubin tests led to a second and more important reason for the use of the
more soluble gas, carbon dioxide, as the insufflating agent.

Nevertheless, in spite of the widespread acceptance of the hazards in-
volved, air and oxygen continue to be used commonly for tubal insufflation as
well as for diagnostic air-contrast studies in the practice of urology and
surgery. Based on a survey of 1,267 urologists, Ramson and co-
workers reported 58 deaths and 64 severe nonfatal cases of gas embolism
resulting from retroperitoneal pneumography. They discovered that air
was by far the most commonly used agent and that only two urologists re-
ported using carbon dioxide as a contrast medium. This paper is a report of
a comparative study carried out in our laboratory demonstrating the median
lethal doses of carbon dioxide and air when injected into the left external
jugular vein of the dog.

Method

A total of 89 mongrel dogs, weighing between 5.1 and 9.7 kilograms, were
used in this experiment. No preanesthetic belladonna drugs were used.
Anesthesia consisted of intraperitoneal pentobarbital, 30 mg. per kilogram of
body weight, and the animals were kept in the supine position throughout the
experiment. On becoming anesthetized, endotracheal intubation was performed
by direct laryngoscopy with a suitable orotracheal catheter, 100 per cent
oxygen was administered, and respirations were controlled with a Bennett
positive-negative phase assistant at a rate between 35 and 40 per minute. Intrapulmonary pressures varied with the size of the animal, ranging between 8 and 10 cm. of water during the positive phase to minus 3 and 4 cm. of water in the negative phase. Tidal exchange was judged adequate by observation of the movements of the thoracic wall, being in all cases in timing with the respirator. A Waters to-and-fro canister filled with high moisture soda lime was utilized for the absorption of endogenous carbon dioxide. A mercury manometer connected through a column of heparin solution to the carotid artery provided a means of monitoring the arterial blood pressure.

![Diagram](image)

Fig. 1.—Scheme of monitoring and pressure injection system. 1. left external jugular vein; 2. carotid artery; 3. Waters to-and-fro canister; 4. Bennett respirator; 5. Heidbrink anesthesia machine with carbon dioxide and oxygen sources and flow meters; 6. three-way stopcocks; 7. injecting syringes; 8. heparin solution; 9. aneroid manometer; 10, mercury manometer; 11, electrocardiograph.

The left external jugular vein was surgically exposed, and a polyethylene catheter was threaded into the vessel a distance of 2 to 3 cm. and then doubly ligated in place. This catheter provided the means of administering the respective gases, and was connected through a three-way stopcock to a pressure-gauge injecting system as schematically diagrammed in Fig. 1. With this setup it was possible to approximate an injection pressure of 200 mm. Hg, which was used in all cases with both of the gases under study. The time of injection varied with the volume of gas used in each case, ranging between 1
and 3 seconds. A single injection was used in each of the 89 dogs, those surviving being sacrificed at the termination of the experiments, when the vital signs had returned toward normal values. The initial dosage schedule pattern used in this experiment followed the method described by Dixon and Mood, referred to by them as the "Up and Down Method." After this method had been used to provide the dosage range in which some animals lived and others died, intermediate doses were selected.

Electrocardiograms, standard lead II, were taken during each of the experiments just prior to, during, and for 15 seconds following the injection of the gases. Subsequent tracings were made 30 seconds after the injection, and then at 1 minute intervals until the animals either died or tracings similar to those of the control period were obtained. The pulse rate was monitored by analysis of the electrocardiograph at the above-mentioned intervals of time.

Dose Response Curves
Air and CO₂

![Graph showing dose response curves for air and CO₂]

Air: LD₅₀ = 5.1 cc/kg
CO₂: LD₅₀ = 25.0 cc/kg

Fig. 2.

Results

Analyzed by the method of statistical analysis proposed by Litchfield and Fertig,¹⁶ the results of the study are presented in Table I. The dosage points and responses that contribute to the computation of the LD₅₀'s (lethal dose for 50 per cent of the animals) have been plotted in Fig. 2. Analysis of these data gives an estimate for the LD₅₀ for air as 5.1 ± 0.5 c.c. per kilogram and for carbon dioxide 25.0 ± 1.7 c.c. per kilogram. These LD₅₀'s are significantly different, and their ratio indicates that air is approximately five times more toxic in its effect than carbon dioxide.
TABLE I. LETHAL DOSAGE FOR DOGS INJECTED WITH AIR AND CARBON DIOXIDE

<table>
<thead>
<tr>
<th>DOSE (C.C./K.G.)</th>
<th>NO. OF DOGS</th>
<th>% DEAD</th>
<th>DOSE (C.C./K.G.)</th>
<th>NO. OF DOGS</th>
<th>% DEAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LIVING</td>
<td>DEAD</td>
<td></td>
<td>LIVING</td>
<td>DEAD</td>
</tr>
<tr>
<td>4.0</td>
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<td>0</td>
<td>0</td>
<td>3.75</td>
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<tr>
<td>4.3</td>
<td>6</td>
<td>5</td>
<td>45.5</td>
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<td>1</td>
</tr>
<tr>
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<td>6</td>
<td>5</td>
<td>43.3</td>
<td>13.3</td>
<td>1</td>
</tr>
<tr>
<td>6.25</td>
<td>4</td>
<td>7</td>
<td>63.6</td>
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</tr>
<tr>
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<td>2</td>
<td>9</td>
<td>81.8</td>
<td>23.9</td>
<td>6</td>
</tr>
<tr>
<td>7.8</td>
<td>0</td>
<td>4</td>
<td>100.0</td>
<td>29.9</td>
<td>2</td>
</tr>
<tr>
<td>LD₉₀</td>
<td>5.1 ± 0.5 C.C./kg.</td>
<td></td>
<td>LD₉₀</td>
<td>25.0 ± 1.7 C.C./kg.</td>
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</table>

Comments

The results of this study have demonstrated that in dogs carbon dioxide has a greater margin of safety than does air. From this a reasonable inference might be drawn that the same situation is present in the human. For this reason carbon dioxide rather than air is recommended for diagnostic studies whenever there is the possibility that there might be entrance of the gas into the vascular compartment of the body. These findings substantiate those of Stauffer and associates, who used carbon dioxide as a contrast material for intracardiac roentgenography. They found that intravenously injected carbon dioxide is well tolerated in the anesthetized laboratory animal. These authors later injected 7.5 c.c. per kilogram of body weight intravenously in infants as intracardiac contrast material, and found that the only physiologic dysfunction noted was a transient apnea. A similar response has been noted in dogs where the same dose of air caused a 100 per cent mortality.

It will be noted that the median lethal dose of air determined in this study is somewhat lower than the lethal-dose range reported in other studies. In an attempt to simulate clinical conditions which lead to gas-embolism accidents, we injected our gases at a constant predetermined pressure of 200 mm. Hg. In this way we believe that the rate of injection was better controlled from animal to animal than by simply injecting rapidly or by injecting the different doses in a specified length of time. That this technique is responsible for the smaller median lethal dose for air is suggested by the stress placed on the rate of injection by numerous investigators. Durant, reporting on the efficacy of the left-side-down position in bringing about recovery following the injection of intravenous air, noted not only the importance of the amount of gas used but also the pressure under which the gas was injected. Richardson and his group likewise found that the rate of injection was of great importance. These investigators found that if the rate was less than 1 c.c. per kilogram per minute large quantities could be tolerated. They described one 23 kilogram animal that received a dose of 1,377 c.c. of air over a period of 460 minutes before dying. Wolfe and Robertson, in contrast to others, felt that the speed of injection was of little significance since, no matter how slowly injected, the air would accumulate in the pulmonary artery and its branches and cause death. They felt that the amount of air necessary to cause death was 0.5 c.c. per kilogram. Our results have confirmed this observation.

All of the patients with the typical of acute embolism common, reaching the heart was the embolus. In the animals with the carbon dioxide group the atrioventricular conduction from either of the two ventricles was normal but only rarely was an arrest noted.

With the following comments, reaching a sudden and crescendo was the embolic phenomenon. The ratio of the animals which suffered a sudden and not a gradual arrest in the heart, which recovered from this shock interval was 1:1. The pre-embolic venous air or carbon dioxide had in many of the animals which recovered, without any permanent results but which evidence of the vital signs assumed.

The results of patients of Moore and Driscoll and the material injected into the intravenous veins of the experimental animals were almost identical. In all cases of both the experimental and patients with carbon dioxide per minute the blood in 15 minutes explained the direct answer of the analogy fold in the ability of the blood.
of air necessary to produce death was proportional to the size of the pulmonary artery and its branches. They found that the lethal dose for the rabbit was 0.5 c.c. per kilogram of body weight, whereas, for the dog they reported a lethal dose in the range of 15 c.c. per kilogram.

All of the animals in our series showed electrocardiographic changes typical of acute cor pulmonale, consisting of an increase in the amplitude of the P waves and deepening of the S waves. These findings were transient in the animals which lived. Such changes were more prominent in the carbon dioxide group than in the group which received air. Varying degrees of atrioventricular heart block occurred in all of the dogs which eventually died from either of the two types of embolism. Among the animals surviving, transient conduction defects were commonly seen in the carbon dioxide group but only rarely in the dogs which lived following intravenous injection of air.

With the higher doses of either gas, the blood pressure dropped immediately following injection. In the carbon dioxide group this drop was precipitous, reaching minimum readings within 5 to 10 seconds, whereas when air was the embolic agent the pressure took 20 to 30 seconds before reaching similar shock levels. The degree of pressure drop in both groups was in proportion to the amount of gas injected. After varying intervals of hypotension, usually lasting between 1 and 2 minutes, the arterial blood pressure of the animals in the carbon dioxide group which eventually recovered showed a sudden and dramatic climb. Values exceeding the control readings were reached in a period of a few seconds. This was in contrast to the animals which recovered from intravenous air whose blood pressures following the shock interval characteristically took 30 seconds to several minutes to reach pre-embolic values. The dogs that died following the injection of carbon dioxide had immediate and severe falls in mean arterial blood pressure. The animals which exhibited profound shock with barely recordable pressures, but which eventually recovered, however, soon showed minimal changes in vital signs and electrocardiographic tracings from the control tracings.

The results reported here are of interest in the light of the findings of Moore and Braselton, who compared carbon dioxide and air as embolic material injected into the pulmonary vein. Utilizing the cat as their experimental animal these workers found that doses of air exceeding 0.25 c.c. per pound of body weight injected into the pulmonary vein would lead in most cases to a typical coronary death. In contrast, the same authors were unable to produce a stable coronary embolus by using as much as 3 c.c. of carbon dioxide per pound. In all cases, the latter gas was entirely taken up by the blood in 15 to 20 seconds, the heart not being visibly affected. Moore explains the difference in toxicity levels of the two gases as being due to the twenty-fold increase in blood solubility of carbon dioxide over air, as well as the ability of the former gas to combine with the alkaline-buffer systems of the blood.
In the present study, death following the intravenous administration of carbon dioxide can most likely be explained from one of three mechanisms or possibly a combination of all three:

1. **Acute Cardiac Dilatation.**—Richardson was the first to note the acute dilatation of the right ventricle and auricle following the intravenous administration of large doses of air. It seems plausible that a similar response would occur after the massive doses of carbon dioxide used in this experiment.

2. **Impaired Coronary Flow.**—The early signs of myocardial ischemia noted on the electrocardiograph following the injection of either air or carbon dioxide would indicate that the coronary flow is markedly impaired. Oppenheimer, Durant, and Lynch, studying the cardiovascular changes in air embolism, have shown a biphasic elevation of the pulmonary arterial blood pressure concomitant with the fall in systemic arterial pressure. Observing a localized right ventricular ischemia in a series of open-chest experiments, these same authors, in explaining the phenomenon, cited the work of Visscher,7 who demonstrated the importance of the pressure gradient between the aorta and the pulmonary artery in maintaining coronary blood flow.

3. **Anemia.**—The large bolus of carbon dioxide injected into the systemic venous system lodges in the pulmonary arterial bed; effective pulmonary circulation ceases. This results in marked impairment of the gas exchange normally carried out between the alveoli and the pulmonary capillaries.

An appreciation of the amount of intravenously injected carbon dioxide necessary to bring about the death of the experimental animal is apparent when one remembers that the average 6 kilogram dog has a blood volume of about 500 c.c. The median lethal dose amounts to 30 per cent of this volume. If such results can be carried over to the human, the L.D₉₀ of intravenous carbon dioxide in a 50 kilogram person would amount to values of 1,200 to 1,300 c.c. It is unlikely that such volumes of carbon dioxide are ever used clinically with the possible exception of the Rubin test. It is common practice in many gynecologic clinics to bring the insufflating pressure repeatedly to 150 to 200 mm. Hg, in an attempt either to open nonpatent Fallopian tubes, or to investigate the possibility of a leak in the Rubin apparatus. When such a practice is carried out, it seems advisable to allow intervals of several minutes to elapse between insufflations while observing the blood pressure closely for any indications of instability.

**Summary**

The median lethal doses of intravenous air and carbon dioxide were determined in 89 mongrel dogs. This study showed that air is approximately five times as toxic as carbon dioxide as an intravenous embolic agent. Blood pressure and electrocardiographic changes are described and possible mechanisms of death are discussed. The relative toxicity differential between the two gases in laboratory animals is offered as evidence for the preferential use of carbon dioxide as an insufflating or gas contrast material in clinical practice.

We wish to express our gratitude to Dr. J. Frank Supplee, III, for his invaluable assistance in interpreting the electrocardiographic tracings.
administration of gas embolism mechanisms

This acute vascular administration response would result in experimental

hemorrhagic noted in carbon or carbon dioxide. Oppenheimer observed. Observing a

shock; changes in air passage, and arteriolar blood flow. Observing a

experiment, the work of this report between normal blood flow.

aortic the systemic arterial and coronary circulatory exchange in cardiopulmonary.

Carbon dioxide was apparent in the blood volume of this volume.

Intravenous injection of 1,200 to 3,600 ml of 4% venesection ever used in clinical practice repeatedly to 300 to 500 ml in 5 to 10 min.

When such venesection in several minutes mortality is reduced closely for

Ninety to 150 ml of Carbon dioxide were approximately adequate in this present. Blood flow in the closeable mechanism between the sharp preferential blood flow in clinical

use of in vitro invaluable

References