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effects of pulmonary gas embolism on circulation and respiration in the dog

FTJ Verstappen

EFFECTS OF PULMONARY GAS EMBOLISM ON CIRCULATION AND
RESPIRATION IN THE DOG

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt
door steun van de Nederlandse Hartstichting.

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on circulation and respiration in
the dog

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CONTENTS

General Introduction	3
Chapter I : Effects on circulation	12
Chapter II : Effects on respiration	35
Chapter III: Excretion of venous gas bubbles by the lung	58
Chapter IV : Origin of arterial hypoxemia during pulmonary gas embolism	75
Chapter V : Gas movement between alveolar space and intra- vascular gas bubbles in the pulmonary circulation	90
Chapter VI : Influence of body position on the effects of pulmonary gas embolism	107
General Conclusions	118
General Summary	121
Algemene Samenvatting	123

GENERAL INTRODUCTION

Pulmonary gas embolism is rarely seen in patients since gas bubbles can penetrate into the venous circulation only if a vein is opened in contact with ambient air. But even so there must furthermore prevail a pressure relationship enabling gas (air) to penetrate into the vascular system rather than blood to leave the vessels. These particular conditions may occur during surgical operations in mediastinum, neck region or epidural sinus, and during curettage. Furthermore pulmonary gas embolism may ensue following diagnostic or therapeutic gas (air, CO₂) injections. In some cases oxygen has been administered intravenously as a therapeutic procedure for a number of diseases (Regelsberger, 1976). Eventually some rare causes of pulmonary gas embolism are the accidental penetration of air by intravenous injections and the aspiration of air during birth in patients with placenta praevia. In most cases the physician will be taken by surprise by such a pulmonary gas embolism. The patient exhibits sudden and apparently unexplained serious symptoms such as dyspnea, cyanosis and loss of consciousness. Since the penetration of the gas (in most cases air) into the venous system often occurs very rapidly and no immediate prevention of further gas penetration or therapy is instituted, pulmonary gas embolism is fatal in many cases. The lethal dose of the penetrating venous gas depends on the following factors: the kind of gas, the speed of penetration, the position of the body and the condition of the patient, particularly concerning circulation and respiration. From animal experiments it may be estimated that in adult man the lethal dose of air venously administered within 10 seconds will be 100 to 300 ml. An early and fast diagnosis is possible from the initial symptoms. Particularly characteristic is a "mill wheel" murmur above the heart. Other symptoms are a consequence of respiratory and circulatory insufficiency. Treatment of pulmonary gas embolism must be initiated by preventing further pe-

netration of gas bubbles (1). This, however, sometimes is very difficult, e.g., during birth in patients with placenta praevia or after curettage. Subsequently the patient should be positioned on his left side since the right ventricle works more effectively in this position (2); the ejection tract then is dependent and therefore filled with blood rather than with gas (Durant et al., 1954; Holt et al., 1966; Cook et al., 1967). If these two measures are not sufficient and there occurs cardiac arrest, immediate cardiac massage and artificial ventilation must be applied (3). Since the right heart and the great veins presumably are filled with gas, aspiration of this gas by cardiac puncture is indicated (4). The effect of artificial ventilation with pure oxygen may be dubious; the hypoxemia ensuing from pulmonary gas embolism may be alleviated but on the other hand a transient increase in the obstruction of the pulmonary circulation may occur (see chapter V). Exposure to a high-pressure chamber may be beneficial since the gas bubbles decrease in size due to the increased pressure and therefore become less voluminous (5); but this is an utopic measure in view of the necessity of fast action. Administration of vasopressor agents is not a causative treatment but may be effective for combating hypotension (6). Gottlieb et al. (1965) compiled from the literature 93 cases of pulmonary gas embolism. 37 out of the 40 untreated patients succumbed. Among the remaining 53 cases the mortality in a group of 27 patients treated by left-side position, oxygen and vasopressor agents, was one third of that in patients treated with only oxygen and vasopressor agents or cardiac massage with open thorax. These authors concluded that left-side positioning is very important in the treatment of pulmonary gas embolism.

There is a form of pulmonary gas embolism not caused by gas penetration through a lesion of a vein, the decompression or caisson disease, where the gas bubbles spontaneously arise in the tissue because the dissolved gas molecules cannot be removed sufficiently

fast by the blood to the lungs. Gas bubbles originate everywhere in the body and lead to a great variety of symptoms. A detailed discussion of this condition, however, is beyond the scope of the present study. A large proportion of the gas bubbles eventually are found in the venous circulation and drift to the lungs (Behnke et al., 1936/36; Buckles, 1968; Cockett and Kado, 1967; Emerson et al., 1967; Heimbecker et al., 1973; Lever et al., 1966; Merrill, 1970). The decompression sickness is primarily treated by recompression which ensures that the gas bubbles decrease in size and possibly are completely redissolved. Subsequent gradual decompression allows the circulation to remove the surplus of gas molecules to the lungs where they are exhaled. The decompression schemes used remain empirical and have resulted in a variety of different tables. Administration of various respiratory gas mixtures, such as oxygen-helium mixture or pure oxygen, is dangerous particularly during the first minutes of changing the gas mixture. As described in chapter V, the gas bubbles, particularly those in the pulmonary circulation, will increase in size and thus further augment the circulatory obstruction. Prevention of decompression sickness therefore is of primary importance. Such preventive measures are easily applicable in professional workers exposed to high pressure (dock workers, tunnel construction, professional divers, space travel), but the increasingly popular diving sport claims more and more victims in spite of enormous efforts of cautioning and prevention by sport organizations.

After this survey of the practical aspects of pulmonary gas embolism we will now review our knowledge of the pathophysiology. The central question is: what happens with the venously administered gas bubbles? Already back in the years between 1930 and 1940 several investigators found that venous gas injections below the lethal dose induced reversible phenomena (review by Bond, 1969). From this it could be concluded that the gas bubbles must have disappeared. Contrary to this situation solid (coagula, glass beads, etc.) and

liquid (fat, amniotic fluid) emboli induced changes which lasted much longer, and could be shown still to be present in the pulmonary circulation much later. The fast disappearance of the symptoms of gas embolism is most easily explained for CO_2 which is well soluble. The disappearance of the other investigated gases O_2 and N_2 could not be demonstrated directly but on theoretical grounds the possible mechanisms must include excretion into the alveolar air, dissolving in blood and adjacent tissues, and passage into the systemic circulation. In chapter III the excretion of venous gas bubbles into the alveolar space is demonstrated. Whether gas bubbles also are able to pass the pulmonary circulation must be doubted on the basis of the available data in the literature (Curtillet, 1939; Knisely et al., 1957; Steffey et al., 1974). The disappearance of the gas bubbles from the pulmonary circulation also explains the changes caused by venous gas injections as found by various investigators (Berglund and Josephson, 1970; Cockett et al., 1968; Mandelbaum and King, 1963). These changes are:

- a) a rapid increase in the pulmonary arterial pressure up to a maximum 30 to 60 s after gas injection; during the following 10 to 15 min the pressure gradually reverts to its original level;
- B) a minor short-lasting decrease of cardiac output and systemic arterial pressure concomitant with a simultaneous small increase in central venous pressure;

C) an unchanged pulmonary wedge pressure and left atrial pressure. All these circulatory changes also agree with the findings of Curtillet (1939) and Knisely et al. (1957) during in vivo microscopy. These authors saw that the gas bubbles were arrested in arterioles of 30 to 40 μm diameter, were deformed into long gas columns, and were locally and gradually absorbed. In summary the course of pulmonary gas embolism may be described on the basis of the aforementioned findings as follows. The gas bubbles are carried by the

blood to the right heart and into the pulmonary circulation. There they are dispersed and arrested in vessels of 30 to 40 μm diameter. Thus they block part of the pulmonary circulatory bed and induce an increase in resistance. This increase in resistance reflects in an increased pulmonary arterial pressure in the presence of an only short-lasting decrease in cardiac output. Since the pulmonary arterial pressure declines again it must be presumed that the excretion of the gas bubbles occurs readily. After about 15 min the pulmonary arterial pressure has returned to its original level, which means that by this time practically all bubbles have disappeared. The suggestion of a vascular activity of the pulmonary circulation remains an unknown factor in this pathophysiological picture.

A new aspect was provided by investigations where the gas was administered not in large amounts (1 to 10 ml kg^{-1}) during a few seconds but rather in small quantities or continuously (0.03 to 0.70 $\text{ml kg}^{-1} \text{min}^{-1}$) during many minutes (Spencer and Oyama, 1971; Steffey et al., 1974; Wycoff and Cann, 1966). Pulmonary arterial pressure gradually increased during the gas administration and reached a constant level after about 15 min. After discontinuing the gas administration the pulmonary arterial pressure returned to its original level. With high infusion rates the aortic pressure decreased and the central venous pressure increased. This points to a decreased cardiac output, probably due to the increased pulmonary vascular resistance. All these findings again suggest a continuous excretion of the gas bubbles from the pulmonary circulation, the excretion reaching an equilibrium with the gas bubbles infused. If the supply surpasses the elimination, the obstruction of the pulmonary circulation increases which may lead to impending insufficiency of the right ventricle. Furthermore Spencer and Oyama (1971) also found a difference in embolizing power between CO_2 , O_2 and N_2 . With the same infusion rates the pulmonary arterial pressure increased more with N_2 than with O_2 , and more with O_2 than with CO_2 . The small effect of CO_2 is explicable by the good solubility of CO_2 as men-

tioned above, but the difference between O_2 and N_2 , which elicits quite similar effects after injection, is less easily explained. For this reason a systematic study was initiated where not only CO_2 , O_2 and N_2 but also He and Ne were examined. The effects of varying rates of infusion and amounts of injection of these gases on the circulation are compared in chapter I.

Although pulmonary gas embolism primarily affects the circulation, there is also a characteristic effect on respiration. Tachypnea, dyspnea, increased airway resistance, decreased lung compliance and hypoxemia are the most important symptoms. Stimulation of lung sensors (irritant receptors) by emboli might elicit reflex activities leading to these phenomena. An argument in favor of this mechanism is, according to Bernthal et al. (1961), the linear relationship between the administered emboli (here glass beads of 75 μm diameter) and the increase in respiratory frequency. Cate et al. (1953) and Marazzini et al. (1966) furthermore found a correlation between the increase in pulmonary arterial pressure and in respiratory frequency. In chapter II similar investigations concerning pulmonary gas embolism are reported. Megibow et al. (1942) and Hirose et al. (1973) showed that the vagal nerve plays an important role in the tachypneic reflex, in that section of both vagi abolished the tachypnea immediately. The literature is unanimous concerning the changes in the mechanical properties of the lungs (airway resistance and lung compliance), we therefore did not determine these properties in the present study. Two chapters (chapter II and IV) are devoted to the pathogenesis of the arterial hypoxemia. The complexity of the gas exchange processes in the lung called for a thorough analysis from which some suggestions for the clinician may be derived. Just as in many other pathophysiological situations the distribution of the ventilation-perfusion ratio in the lung plays a key role here too.

The last two chapters deal with the influence of various breath-

ing gas mixtures (V) and of body position (VI) on the effects of pulmonary gas embolism. The results obtained appear to be important for the treatment of pulmonary gas embolism.

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CHAPTER I

EFFECTS ON CIRCULATION

SUMMARY

Mongrel dogs weighing 15 to 25 kg and anesthetized with thio-pental/gamma-hydroxybutyric acid were used to investigate the effects of pulmonary gas embolism on pulmonary arterial pressure (P_{ap}), systemic arterial pressure (P_a) and cardiac output ($\dot{Q}$). Pulmonary gas embolism was produced either by venous injection or by venous infusion. The most marked effect of pulmonary gas embolism on circulation was an increase in P_{ap} which returned to the original level after stopping the gas administration.

1. After gas injection P_{ap} rose to a maximum within 30 to 60 s. The extent of this rise in P_{ap} showed a positive correlation with the volume of the injected gas. The kind of gas (oxygen, helium, neon, nitrogen, air), however, did not influence the extent of the rise in P_{ap} , but it did influence the time of return of P_{ap} to the original level. Carbon dioxide showed an exceptional behavior in that it had almost no effect on P_{ap} at all. P_a hardly changed with the volume of the gas injections (20 to 60 ml injected within 1 s); $\dot{Q}$ was not measured after gas injections (the direct Fick method is not usable in this situation).

2. Gas infusion caused a slow rise of P_{ap} , its steepness and extent depending on the rate of infusion and on the physical properties of the infused gas. When the right ventricle was able to maintain its output, a constant level of P_{ap} was reached after 10 to 15 min. In this circulatory steady state P_{ap} appeared to be a measure of the degree of embolization. However, this relationship no longer held when the right ventricle failed as evidenced by a fall in P_{ap} , P_a and $\dot{Q}$.

It may be concluded that pulmonary gas embolism produces a transient partial obstruction in the pulmonary circulation and that the performance of the right ventricle determines the maximum degree of embolization compatible with a sufficient circulation.

Key words: Gas embolism - pulmonary embolism - pulmonary arterial pressure.

INTRODUCTION

In 1670 Robert Boyle discovered bubbles in the circulation during decompression experiments; he may have been the first investigator in the field of gas embolism. In 1889 Hare mentioned a report of Magendie who introduced 40 to 50 pints of air into the veins of a horse without causing immediate death (referred to by Bond, 1969). In the years thereafter investigators restricted themselves to the study of the lethal dose of venous injection for various gases in different animals (reviewed by Bond, 1969; Harkins and Harmon, 1934; Richardson et al., 1937; Wolffe and Robertson, 1935). After the Second World War measurements of several circulatory and respiratory variables were made during venous gas embolism. Most of the investigations were performed with gas injections, probably to imitate pulmonary gas embolism as found in patients. The following results were obtained:

- A) a rapid increase in pulmonary arterial pressure (P_{ap}) reaching a maximum within 30 to 60 s after the gas injection, followed by a slow decrease to the original level within 10 to 15 min;
- B) a small short-lasting decrease of cardiac output ($\dot{Q}$) and systemic arterial pressure (P_a) with a synchronous small rise of central venous pressure;
- C) an unchanged pulmonary wedge pressure and left atrial pressure (Berglund and Josephson, 1970; Cockett et al., 1968; Deal et al., 1971; Gilbert et al., 1968; Josephson, 1970a, 1970b, Mandelbaum and King, 1963).

Much less work has been done concerning the effects of venous gas infusion. Increase in systolic right ventricular pressure and in systemic venous pressure, decrease in pulmonary blood flow and

an unchanged or decreased systemic arterial pressure during venous gas infusion have been reported (Spencer and Oyama, 1971; Steffey et al., 1974; Wycoff and Cann, 1966). The degree of the circulatory changes was dependent on the kind (CO_2 , O_2 and N_2) and dosage of the gas infused.

In the present paper the circulatory effects of pulmonary gas embolism are described, produced either by venous injection of various volumes of different gases or by various rates of venous infusion of these gases.

METHODS

Mongrel dogs of either sex, weighing 15 to 25 kg, were used. Half an hour before anesthesia 0.5 mg of atropine sulfate and 2 mg of droperidol were injected intramuscularly. Anesthesia was induced by intravenous injection of 250 mg kg^{-1} gamma-hydroxybutyric acid and 20 mg kg^{-1} thiopental, and maintained by infusion of a solution containing a mixture of 95% gamma-hydroxybutyric acid (200 g l^{-1}) and 5% thiopental (10 g l^{-1}) at a rate established empirically (about 0.2 ml min^{-1}). The animals were heparinized. When artificial ventilation was applied, the muscles were paralyzed by 2 mg diallyl-bis-nortoxiferine; the administration of this dose was repeated if necessary. In order to eliminate the well-known influence of body position on the effects of venous gas administration (Cook et al., 1967; Durant et al., 1947, 1954; Holt et al., 1966) our experiments were performed in supine animals throughout. The trachea was intubated; a catheter (USCI nr. 6 5400) was introduced into the femoral artery and the tip moved into the abdominal aorta; another catheter (USCI nr. 8 5431) was inserted into the left femoral vein and the tip moved into the pulmonary artery under X-ray control; a transparent catheter was placed in the right femoral vein for infusion. A Harvard respirator (model nr. 607) was used when artificial

ventilation was applied. Braun infusors (Melsinger Unita 2B) were used for infusion of bubbles and anesthetics. Blood pressure in pulmonary artery and aorta was continuously measured by Statham pressure gauges (model nr. P23Db) and recorded on a UV-recorder (Honeywell Visicorder model 1108). Heart frequency was obtained from this record. Cardiac output during steady state was calculated from Fick's principle:

$$\dot{Q} = \frac{\dot{V}_{O_2}}{C_{aO_2} - C_{\bar{V}O_2}} \quad \dot{Q} = \text{blood flow in l min}^{-1}, \dot{V}_{O_2} = \text{O}_2 \text{ consumption in ml min}^{-1}, C_{aO_2} \text{ and } C_{\bar{V}O_2} = \text{O}_2 \text{ concentration of arterial and mixed venous blood, respectively, in ml l}^{-1}.$$

$\dot{V}_{O_2}$ was calculated with the equation $\dot{V}_{O_2} = \dot{V}_E (F_{IO_2} - F_{EO_2})$. $\dot{V}_E$ (expiratory gas volume in ml min⁻¹ corrected to BTPS) was measured by a spirometer and F_{IO_2} and F_{EO_2} (inspiratory and expiratory O₂ volume fraction, respectively) were measured by Scholander analysis. In order to determine C_{aO_2} and $C_{\bar{V}O_2}$ blood samples were taken from the catheters simultaneously with the collection of expiratory gas. These samples were analyzed for hemoglobin concentration (by HiCN method), oxygen pressure (Gasmonitor, Radiometer, Copenhagen) and pH (pH meter 22, Radiometer, Copenhagen). Oxygen saturation was calculated, after correction of the P_{O₂} to body temperature (measured in the rectum by a mercury thermometer), from the nomogram constructed by Rossing and Cain (1966). When oxygen was used as infusion gas, the Fick principle remained valid because the infused amount of oxygen never exceeded 3% of the total oxygen consumption. At the end of several experiments post-mortem examination was carried out with special attention paid to the macroscopic anatomy of heart and lungs, particularly concerning the possible presence of intracardiac shunts, atelectasis and lung edema.

RESULTS

A. Intravenous infusion of gases at different rates.

The most marked effect of intravenous gas infusion is that on pulmonary arterial pressure (P_{ap}). Fig. 1 shows the results of a typical experiment; $P_{apdiast}$ is plotted against time for O_2 infusion at a rate of 2.0, 3.75, or 5.0 ml min⁻¹. The rate of increase as well as the maximum level of $P_{apdiast}$ depend on the rate of infusion. After stopping the gas infusion $P_{apdiast}$ returns to control level. Fig. 2 shows the rise of $P_{apdiast}$ with an infusion of neon at 1.6, 2.4, or 3.2 ml min⁻¹. In Table 1 the results of statistical analysis are presented. Symbol A denotes the ratio of a variable as measured during gas infusion after reaching a constant level and as measured before gas infusion. $A_{P_{ap}}$ is linearly related to the rate of infusion as is illustrated for oxygen and neon in Fig. 3. Systemic arterial pressure (P_a) and cardiac output ($\dot{Q}$) hardly change except in some cases during infusion of 3.2 ml min⁻¹ of neon or nitrogen. The latter situation is shown in Fig. 4. For nitrogen $P_{apdiast}$ during gas infusion does not reach a constant level, but falls precipitously after a peak; P_{adiast} decreases synchronously. When $\dot{Q}$ is measured several minutes later, there is a fall by 1.6 l min⁻¹ during neon infusion and by 2.1 l min⁻¹ during nitrogen infusion. The point of reversal in P_{ap} might indicate beginning right ventricular insufficiency. Thus the value of $A_{\dot{Q}}$ in Table 1 is significantly lower during infusion of 3.2 ml min⁻¹ neon because of impending circulatory failure in some of the experiments. Heart frequency changed only in 14 out of 264 measurements as could be expected due to atropinization of the animals. Pulmonary arterial and systemic arterial pulse pressure did not change at all except when $P_{apdiast}$ was very high (> 25 mmHg); in these latter cases pulmonary arterial pulse pressure increased.

Fig. 1

Effect of venous oxygen infusion at different rates on diastolic pulmonary arterial pressure.

Fig. 2

Effect of venous neon infusion at different rates on diastolic pulmonary arterial pressure.

TABLE 1

Effects of various venous gas infusions on circulation.

Gas infusion	$A \frac{P_{ap}}{P_s} = \frac{\text{mean pulmonary arterial pressure during gas infusion}}{\text{mean pulmonary arterial pressure in control condition}}$	$A \frac{P_s}{P_s} = \frac{\text{mean systemic arterial pressure during gas infusion}}{\text{mean systemic arterial pressure in control condition}}$	$A \frac{Q}{Q} = \frac{\text{cardiac output during gas infusion}}{\text{cardiac output in control condition}}$
2 ml min ⁻¹ O ₂ N = 11	1.351 S.E. = 0.029	1.002 S.E. = 0.021	
3.2 ml min ⁻¹ O ₂ N = 20	1.477 S.E. = 0.076	1.009 S.E. = 0.012	0.982 S.E. = 0.025
5 ml min ⁻¹ O ₂ N = 17	1.772 S.E. = 0.055	0.977 S.E. = 0.020	
2.4 ml min ⁻¹ Ne N = 10	1.739 S.E. = 0.031	0.981 S.E. = 0.062	0.981 S.E. = 0.052
3.2 ml min ⁻¹ Ne N = 17	1.951 S.E. = 0.037	0.965 S.E. = 0.046	0.799 S.E. = 0.089

Figures are mean value $\pm$ standard error (S.E.); N = number of experiments.

Control data were measured before gas infusion, the data during gas infusion 15 min after starting the infusion.

Fig. 3

Ratio $A \frac{P_{ap}}{P_s}$ of mean pulmonary arterial pressure as measured during gas infusion after reaching a steady state and as measured before gas infusion plotted against rate of infusion.

Fig. 4

Effects of 3.2 ml min^{-1} infusion of N_2 and Ne on circulatory variables

B. Intravenous infusion of oxygen, carbon dioxide, helium, neon and nitrogen at the same rate.

Fig. 3 showed that oxygen and neon cause a different increase of P_{ap} with the same rate of infusion. Intravenous infusions of oxygen, helium, neon and nitrogen at 3.2 ml min^{-1} have different effects on the rate of increase and on the maximum level of P_{ap} (Fig. 5). When P_{ap} did not reach a constant level and rose to an extremely high value, it was decided to stop the gas infusion to prevent circulatory insufficiency, as shown in Fig. 4. CO_2 did not elicit any effect on the circulation.

C. Intravenous injection of different volumes of air.

The effects of various volumes of gas injection on P_{ap} are comparable with different rates of gas infusion. In Fig. 6 the effects of 12.5, 25, 37.5, or 50 ml air, injected intravenously within one second, on diastolic and systolic P_{ap} are shown. The measuring points were taken during the end-expiratory phase of the breathing cycle (the animal was ventilated artificially). There is a marked relationship between the injected gas volume and the rate of increase of P_{ap} as well as the maximum reached. P_{apsyst} and $P_{apdiast}$ change in such a way that pulmonary arterial pulse pressure increases immediately after injection. The extent of this increase depends on the injected gas volume. Subsequently pulmonary arterial pulse pressure returns to its original value within one minute. Mean P_{ap} reaches its maximum after 30 to 60 s and then slowly returns to the original level within 10 to 20 min (not shown in Fig. 6). $\dot{Q}$ cannot be measured by the Fick principle under these circumstances due to the absence of a steady state. But because mean P_a and systemic arterial pulse pressure do not change appreciably, it is unlikely that $\dot{Q}$ changed much.

Fig. 5

Effect of venous infusion of various gases on diastolic pulmonary arterial pressure. Infusion of nitrogen and neon was stopped prematurely because of impending right ventricular failure.

Fig 6

Effect of venous air injection of different volumes on systolic and diastolic pulmonary arterial pressure. The measurements were made during the end-expiratory phase of the respiratory cycle (constant artificial ventilation).

D. Intravenous injection of the same volume of carbon dioxide, oxygen, helium, neon, or air.

The most remarkable observation is the discrepancy between the effects of gas infusion and gas injection. Different gases infused at the same rate induce different changes in P_{ap} (Fig. 5), whereas different gases injected at the same volume cause almost the same changes in P_{ap} (Fig. 7), CO_2 being a notable exception. Injection of CO_2 causes only a small increase of P_{ap} which disappears within 20 s (Fig. 7). The return of P_{ap} to the original level is not shown in Fig. 7. The rate of decrease of P_{ap} after the maximum is different for the gases used. The original P_{ap} levels are reached after injection of O_2 , He, Ne, or air within 10, 12, 17, and 19 min, respectively.

E. Post-mortem examination of heart and lungs.

Only a few times edema and/or atelectasis was found macroscopically in one or two lobes. The rest of the preparations were normal.

Fig. 7

Effect of venous injection of the same volume of different kinds of gases on systolic and diastolic pulmonary arterial pressure. The measurements were made during the end-expiratory phase of the respiratory cycle (constant artificial ventilation).

DISCUSSION

The main findings of this study are that during venous gas infusion P_{ap} increases, reaches a plateau, and after termination of the infusion returns to control level; after gas injection P_{ap} rises much more rapidly, shows a flat peak, and subsequently returns to the original value. The increase in P_{ap} due to venous gas administration is a direct reflection of increasing pulmonary vascular resistance as long as cardiac output remains constant (resistance = pressure/flow). The resistance in the pulmonary circulation will increase when the bubbles mechanically block parts of the pulmonary circulation (possibly enhanced by vasomotor reaction). Knisely et al. (1957) found that the infused bubbles drift with the venous blood to the right heart and subsequently are pumped into the pulmonary circulation where they are arrested in arterioles. With continuing gas infusion more and more arterioles will be obstructed so that the pulmonary vascular resistance keeps increasing during the first 15 min. Thereafter P_{ap} reaches a plateau which means that the pulmonary vascular resistance does not increase further in spite of continued gas infusion. The increasing number of bubbles in the pulmonary circulation also enlarges the area of contact between the intravascular bubbles and the alveolar space and thus promotes diffusional exchange across the vessel walls. Since the total gas pressure in the bubbles (atmospheric plus pulmonary arterial pressure) exceeds the gas pressure in the alveolar space (atmospheric), net movement of gas from the intravascular bubbles to the alveolar space will be enhanced. When P_{ap} has reached a constant level, bubble removal will equal bubble supply. The maximum rate of bubble excretion is determined by right ventricular performance in maintaining an increased P_{ap} . After stopping bubble infusion the bubble removal continues but its rate will decrease due to decreasing P_{ap} and decreasing area of gas exchange between the intravascular bub-

bles and the alveolar space.

It is evident from the results with infusion of oxygen and neon at different rates (Results A) that the increase of P_{ap} depends on the rate of gas infusion. The rate of infusion has been empirically limited to those values at which the right ventricle is still able to maintain its output in spite of the increasing resistance in the pulmonary circulation. If this limit is surpassed many factors like acidosis, hypoxemia, hypotension, and hypercapnia may influence the results. Only three comparable investigations could be found in the literature. Spencer and Oyama (1971) infused 0.03, 0.09, and 0.15 ml $kg^{-1} min^{-1}$ of CO_2 , O_2 and N_2 into the caval vein of unanesthetized sheep. The gas was not infused continuously but was administered intermittently every minute during 30 min. Their results agree with ours. Wycoff and Cann (1966) infused 0.13 to 0.69 ml $kg^{-1} min^{-1}$ of air into the jugular vein of dogs anesthetized with thiopental. Their conclusion was that 0.13 to 0.61 ml $kg^{-1} min^{-1}$ of air infusion caused systemic arterial hypotension and a small increase of the central venous pressure, which disappeared after stopping the gas infusion; infusion of 0.69 ml $kg^{-1} min^{-1}$ of air resulted in heart failure as evidenced by a large increase of the central venous pressure and irreversible systemic arterial hypotension. The differences in the method (discontinuous measurements) do not allow a comparison with our findings. Furthermore, the used infusion rates were higher than in our experiments. Steffey et al. (1974) infused 3.5 and 7.0 ml min^{-1} of air intravenously in dogs anesthetized with halothane. The air infusion was continued until mean arterial pressure was decreased to 60% of the original value. Simultaneously mean right ventricular pressure increased by 38 to 86% as compared with control data. Oxygen breathing doubled the volume of air infusion required during air breathing to produce a 40% decrease in mean arterial pressure but there was no difference in the spontaneous rate of return of

mean arterial pressure to 90% of control.

From the fact that a plateau of P_{ap} is reached during gas infusion in spite of continuing supply of gas bubbles, and that the circulatory changes produced by the infusion are completely reversible, it must be concluded that all bubbles eventually disappear from the lungs. This disappearance might be explained in several ways:

- 1) the bubbles are forced through the pulmonary capillaries into the pulmonary veins;
- 2) the bubbles disappear from the pulmonary arterioles because the gas slowly dissolves in the surrounding tissue and diffuses into the alveolar space;
- 3) the bubbles pass through arterio-venous communications in the pulmonary circulation;
- 4) a combination of these possibilities.

Experiments with different gases infused at the same rate might provide some indication as to these theoretically possible mechanisms. Such infusions produce a different degree of obstruction in the pulmonary vessels as evidenced by a different response of $P_{apdiast}$ (Results B, Fig. 5), suggesting an influence of the nature of the gas. If dissolving of the gas in the tissue and diffusion into the alveolar space were mainly responsible for the disappearance of the gas, $P_{apdiast}$ should be expected to be related to the diffusive properties of the gas, i.e. the diffusive resistance should be related to the amount of gas remaining in the vessels and thus to $P_{apdiast}$. It has been shown by several authors (Duling and Berne, 1970; Jameson, 1963) that the arteriolar walls are permeable for gases and thus may participate in gas exchange. Krogh's diffusion coefficient (K), being the product of diffusion coefficient (D) and solubility coefficient (α), is a measure of the diffusive conductivity of a medium for a particular gas and should therefore determine the rate of gas transport between the intravascular bub-

bles and the alveolar space. However, no data of K in lung tissue for the gases used here could be found in the literature. Therefore K was calculated from $D \times \alpha$. The solubility coefficients of the gases in water were used for lack of their values in tissue. The values of the diffusion coefficients were taken from Kawashiro et al. (1975). Table 2 shows that the values of Krogh's diffusion coefficient are inversely related to $P_{ap\text{diast}}$ after infusion of 3.2 ml min^{-1} of O_2 , He, Ne, and N_2 during 10 min. However, as mentioned there should be a direct relationship between diffusive resistance ($1/K$) and $P_{ap\text{diast}}$ if our assumption is correct that the gases do escape into the alveolar space. Fig. 8 shows that there is indeed a linear relationship between $1/K$ and $P_{ap\text{diast}}$.

Another way of disappearance of the bubbles, i.e. across the pulmonary capillaries into the pulmonary veins, cannot be excluded a priori but seems unlikely on the basis of the relationship shown above and of the fact that the physical properties of these gases (e.g. the surface tension) may not be expected to differ in a way compatible with our findings. The possibility of an escape of the bubbles through arterio-venous communications can be discounted with even more certainty since such channels could not be demonstrated anatomically in the dog.

Another question is whether vasoconstriction in the pulmonary circulation occurs during pulmonary gas embolism. The investigations as to the occurrence of a vasoconstrictor component have not yet led to a generally accepted opinion. If one accepts that bubbles of inert gases should produce the same stimulus for a nervous or humoral vasoconstriction the same rate of infusion should induce the same increase of resistance. This, however, is contradicted by our experimental results (Fig. 5).

Changes of P_{ap} caused by intravenous gas injections are described in Results C and D. Gas injection causes an acute obstruction of many pulmonary arterioles, so that P_{ap} rises very fast and very

Comparison of the physical properties of various gases and their embolizing effect.

Gas	Diffusion coefficient in water at 37° C in $\text{cm}^2 \text{ s}^{-1}$ (D)	Solubility coefficient in water at 37° C in $\text{ml ml}^{-1} \text{ atm}^{-1}$ (α)	Krogh's diffusion constant in water at 37° C in $\text{ml s}^{-1} \text{ cm}^{-1}$ atm^{-1} ($K = D \times \alpha$)	P_{adialast} (mmHg) after infusion of 3.2 ml min^{-1} during 10 min (Fig.5)
Oxygen	30.5×10^{-6}	236×10^{-4}	72×10^{-8}	19.5
Helium	66×10^{-6}	87×10^{-4}	57.4×10^{-8}	22
Neon	50×10^{-6}	98×10^{-4}	49×10^{-8}	26.5
Nitrogen	29×10^{-6}	126×10^{-4}	36.5×10^{-8}	32.5

D values were obtained from the diagram of Kawashiro (1975) plotting diffusion coefficient against the molecular diameter of the various gases (Radford, 1964). Solubility coefficients were taken from the Handbook of Chemistry and Physics (1960-1961).

Fig. 8

Plot of diffusive resistance of water for gases ($1/K$, K = Krogh's diffusion coefficient) against diastolic pulmonary arterial pressure obtained after 10 min of venous infusion of various gases at the same rate (Fig. 5).

high (compared with gas infusion). If the right ventricle is able to maintain its output, the increased P_{ap} will provide for a fast disappearance of the bubbles. The volume of injected gas will determine the degree of obstruction, as could be confirmed in Results C. The kind of gas is not important for the maximum value of the resistance of the pulmonary vessels, unless the solubility of the gas is so high that part of the bubbles have already disappeared before the sites of obstruction are reached, as may hold for CO_2 . The other gases, O_2 , He, Ne, and N_2 , will cause the same maximum degree of acute obstruction if the same volumes are injected, but the rate of disappearance again depends on the diffusive properties of the gas (see Table 2), as may be seen from the sequence of the disappearance times mentioned at the end of section D of Results.

The most comparable investigation is that of Josephson (1970a). Apart from similar results concerning the circulatory variables, he showed by angiographic examination that injection of air into the pulmonary artery causes an increased diameter of the central pulmonary arteries due to the increasing P_{ap} , a decrease of the emptying rate of the pulmonary arteries due to a partial obstruction of the pulmonary circulation, and a shortened artery-to-vein transit time through the open vessels due to the increased P_{ap} . The vasoconstriction claimed by him, however, does not agree with our findings. Apart from the lack of evidence for a reflex of general vasoconstriction in the pulmonary circulation, one wonders what the meaning of such a reflex might be (Cook et al., 1967; Daily et al., 1966; Daley et al., 1951; Gilbert et al., 1968; Holt et al., 1966; Knisely et al., 1957; Williams et al., 1969).

The observations from the post-mortem examination agree with Dahlgren and Josephson (1970). Furthermore these authors found, by microscopic examination of material from 28 dogs, in 7 cases a small and in 5 cases a moderate degree of pulmonary edema; but there was no relation to the amount of injected air, the increase of P_{ap} ,

or the duration of anesthesia.

Intravenous gas injection repeated daily for a long time (months) elicits anatomical changes of the pulmonary vessels corresponding to the pathology of primary pulmonary hypertension. The great difference, however, is the reversible character of the anatomical changes after stopping the gas injections (Boerema, 1962; Gilbert et al., 1968; Wright, 1962).

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CHAPTER II

EFFECTS ON RESPIRATION

SUMMARY

In mongrel dogs weighing 15 to 25 kg and anesthetized with thiopental/gamma-hydroxybutyric acid the effects of venous gas infusion and injection on several respiratory variables were investigated. During spontaneous respiration pulmonary gas embolism caused an increase of the ventilatory minute volume depending on the degree of embolization. The contribution of breathing frequency and tidal volume to the increase of ventilatory minute volume varied from one animal to the other. During constant artificial ventilation pulmonary gas embolism impaired the pulmonary gas exchange depending on the degree of embolization. How far a steady-state phase in gas exchange can be reached during continuous venous gas infusion depended on the adaptation of the circulation. At severe degrees of embolization circulation as well as gas exchange became deficient. Increasing artificial ventilation during pulmonary gas embolism improved the wash-out of carbon dioxide, but hardly affected the uptake of oxygen. The most important origin of the disturbed gas exchange in pulmonary gas embolism seemed to be an increased inequality of the ventilation-perfusion ratio distribution.

Key words: gas embolism - pulmonary embolism - gas exchange - ventilation-perfusion ratio.

INTRODUCTION

The most prominent effects of pulmonary embolism are tachypnea, polypnea, dyspnea, increased airway resistance, decreased compliance of the lung, and arterial hypoxemia (Behnke et al., 1935/1936; Bernthal et al., 1961; Byrne et al., 1953; Caldini, 1965; Cate et al., 1953; Derks and Peters, 1974; Dick, 1939; Goodwin and Harmel, 1949; Gootman et al., 1962; Halmagyi et al., 1963; Hirose et al., 1973; Horres and Bernthal, 1961; Khan et al., 1972; Levy et al., 1963; Marazzini et al., 1966; Megibow et al., 1942; Mills et al., 1969; Nadel et al., 1964; Sasahara et al., 1967; Whitteridge, 1950; Williams, 1956; Wolffe and Robertson, 1935). The changes in ventilation and lung mechanics during pulmonary embolism may be induced by a stimulation of lung receptors (irritant receptors). Bernthal et al. (1961), Cate et al. (1953) and Marazzini et al. (1966) found a relationship between the amount of compact emboli, the increase in pulmonary arterial pressure (P_{ap}) and the increase in breathing frequency. In this study the same relationship is investigated using gaseous emboli.

The second part of this study is devoted to the pulmonary gas exchange during pulmonary embolism. A relationship could be demonstrated between the degree of pulmonary gas embolism and the degree of arterial hypoxemia during constant artificial ventilation. In the literature the following possibilities are mentioned as a cause of arterial hypoxemia: opening of arterio-venous anastomoses in the pulmonary circulation; alveolar hypoventilation; atelectasis; decreasing diffusing capacity; and unfavorable ventilation-perfusion ratio distribution.

There is indirect evidence from this study that a more unfavorable ventilation-perfusion ratio distribution during pulmonary gas embolism is the major factor causing arterial hypoxemia and hypercapnia.

METHODS

Anesthesia and preparation of the experimental animals were described (see chapter I). The following respiratory variables were recorded on a UV-recorder (Honeywell Visicorder, model 1108): pneumotachogram (pneumotachograph, Elema, Copenhagen), capnogram from an infrared CO₂ analyzer (capnograph, Uras, Hartman and Braun), and oxygrams from polarographic electrodes located in the abdominal aorta and in an outlet from the tracheal tube. The PO₂ electrode in the arterial blood had a response time for 95% deflection of 0.4 s. It was insensitive to pressure and moderate acceleration of the blood and had a stability of 0.5% during 10 h (Kimmich and Kreuzer, 1969a). The PO₂ electrode in the gas phase was placed between the tracheal tube and the heated pneumotachograph. The temperature of the passing air at the electrode could be held constant in this way. The response time for 95% deflection was 0.1 s; the stability was within 0.5% during 10 h (Kimmich and Kreuzer, 1969b). Furthermore, samples were taken from arterial and mixed venous blood for analysis of PO₂, PCO₂ and pH (Gas monitor and pH meter 22, Radiometer, Copenhagen). The circulatory variables of pulmonary arterial pressure, systemic arterial pressure and cardiac output were measured (as described in chapter I) to serve as a circulatory measure of the degree of embolization.

RESULTS

A. Effects of pulmonary gas embolism on respiratory variables during spontaneous ventilation.

In Table 1 breathing frequency and minute volume after intravenous administration of 2 ml min⁻¹ O₂, 5 ml min⁻¹ O₂, 5 ml min⁻¹ He and

5 ml min⁻¹ air during 15 min are compared with the values before the gas infusion. Infusion of 5 ml min⁻¹ O₂ induces a larger increase of ventilation than infusion of 2 ml min⁻¹ O₂. O₂ and He cause similar changes in ventilation during infusion of 5 ml min⁻¹ but 5 ml min⁻¹ air produces a much larger increase of ventilation. This is in agreement with the degree of embolization as seen from the increase of P_{ap} (see chapter I). The large standard errors in the increase of breathing frequency and of minute volume during venous gas infusion indicate the individual differences of changes in ventilation in different dogs; some dogs preferentially respond by an increase in breathing frequency and other by an increase in tidal volume. The gas exchange in the lungs during pulmonary embolism is impaired as reflected by the increasing alveolar-arterial pressure differences of O₂ and CO₂. In spite of hyperventilation the arterial oxygen pressure (P_{aO₂}) is always decreased and the arterial CO₂ pressure (P_{aCO₂}) is increased in most cases. No relation between the extent of embolization and arterial blood gases can be found, because concomitant changes of pulmonary perfusion and ventilation will affect the arterial gas pressures in an unpredictable way.

Two records of changes in circulation and ventilation caused by venous gas injection (50 ml CO₂ and 50 ml O₂) are shown in Figs. 1 and 2. CO₂ causes an increase in P_{ap} of a few mmHg about 3 s after the injection. Within 60 s P_{ap} has returned to its initial level. P_a shows an almost identical reaction. After O₂ injection P_{ap} rises much higher to a maximum around the 47th s, which is in the range between 30 and 60 s as previously found for the maximum (see chapter I). Then P_{ap} slowly decreases to its initial level within 15 min. P_a only shows a short-lasting decrease from 20 to 50 s after the injection. Heart frequency is markedly reduced from 10 to 40 s, which is only seen in this experiment. The ventilatory changes due to CO₂ and O₂ injection are different too. CO₂

causes a transient increase in breathing frequency and tidal volume which starts about 10 s after the injection, but 10 to 15 s later the original values are reached again. Alveolar CO₂ fractional concentration is increased until the end of the polypneic phase. About 8 s after the O₂ injection breathing becomes rapid and shallow. After an apneic phase of 25 s the breathing pattern becomes irregular for many minutes before the original ventilation is re-established. The alveolar CO₂ fractional concentration is lowered even after the apneic phase.

TABLE 1: Effects of venous infusion of various gases on ventilation.

Gas infusion	$A_f = \frac{\text{breathing frequency during gas infusion}}{\text{control breathing frequency}}$	$A_v = \frac{\text{minute volume during gas infusion}}{\text{control minute volume}}$
2 ml min ⁻¹ O ₂ N = 11	1.332, SE = 0.083	1.177, SE = 0.048
5 ml min ⁻¹ O ₂ N = 14	1.780, SE = 0.353	1.542, SE = 0.097
5 ml min ⁻¹ He N = 6	1.710, SE = 0.205	1.600, SE = 0.147
5 ml min ⁻¹ air N = 6	2.270, SE = 0.268	1.942, SE = 0.196

Control data were measured before gas infusion, data during gas infusion 15 min after starting gas infusion.

Fig. 1

Effects of venous injection of 50 ml CO_2 on several circulatory and respiratory variables during spontaneous ventilation. Tracings from top to bottom are capnogram, integrated pneumotachogram, systemic arterial blood pressure and pulmonary arterial blood pressure.

Fig. 2

Effects of venous injection of 50 ml O_2 on several circulatory and respiratory variables during spontaneous ventilation. Tracings from top to bottom are capnogram, integrated pneumotachogram, systemic arterial blood pressure and pulmonary arterial blood pressure.

B. Effects of pulmonary gas embolism during constant artificial ventilation

1. During venous gas infusion.

The gas exchange in the lungs with constant artificial ventilation is impaired during venous gas infusion. As shown in Table 2, the degree of impairment is related to the increase in P_{ap} . The increased alveolar-arterial O_2 pressure difference ($(A-a)D_{O_2}$) is mainly due to a decrease of P_{aO_2} and less to an increase of P_{AO_2} (Table 2a). The increased arterio-alveolar CO_2 pressure difference $(a-A)D_{CO_2}$ shows a similar pattern (Table 2b). The data in Table 2 are expressed in relative values and therefore the change in P_{ACO_2} appears to be larger than that in P_{AO_2} with the same degree of pulmonary gas embolism. Figs. 3 and 4 show the changes in respiratory variables during a moderate degree (infusion of $3.2 \text{ ml min}^{-1} O_2$) and a severe degree (infusion of 3.2 ml min^{-1} air) of pulmonary gas embolism. Fig. 3 demonstrates that the changes of the respiratory variables occur synchronously with the change in P_{ap} and reach a steady level after about 15 min. $\dot{Q}$ is not changed. However, during severe embolization no steady level of P_{aO_2} and P_{aCO_2} is reached within the time of observation in spite of a constant P_{ap} (Fig. 4), and $\dot{Q}$ slowly decreases from 4.0 to 3.3 l min^{-1} during this period. Another interesting phenomenon is the appearance of irregularities in the end-expiratory part of the breathing curves of O_2 and CO_2 rather than a smooth plateau during venous gas infusion (Fig. 5). These irregularities increase with the degree of embolization and disappear again after stopping the gas administration. Furthermore, the maximum levels of F_{AO_2} and F_{ACO_2} during successive expirations vary during the venous gas infusion.

TABLE 2a

Effects of infusion of various gases on pulmonary oxygen exchange during constant artificial ventilation.

Gas infusion	(A-a)D _{O₂} mmHg		P _{A_{O₂}} infusion	P _{A_{O₂}} infusion	P _{ap} infusion
	Control	Infusion	P _{A_{O₂}} control	P _{A_{O₂}} control	P _{ap} control
3.2 ml min ⁻¹ O ₂ N=22	121.3-91.2=30.1 S.E.=2.6	123.7-73.6=50.1 S.E.=2.8	1.020 S.E.=0.009	0.807 S.E.=0.017	1.477 S.E.=0.076
3.2 ml min ⁻¹ He N=11	124.1-93.4=30.7 S.E.=2.3	127.6-73.4=54.4 S.E.=3.6	1.030 S.E.=0.012	0.786 S.E.=0.025	1.584 S.E.=0.051
3.2 ml min ⁻¹ Ne N=14	119.6-87.1=32.5 S.E.=2.8	123.6-58.6=65.0 S.E.=2.3	1.033 S.E.=0.015	0.673 S.E.=0.025	1.951 S.E.=0.037
2.4 ml min ⁻¹ Ne N=13	122.1-90.1=32.0 S.E.=3.7	124.8-70.4=54.4 S.E.=3.8	1.022 S.E.=0.008	0.781 S.E.=0.013	1.739 S.E.=0.031

Alveolar-arterial O₂ difference [(A-a)D_{O₂}], alveolar O₂ pressure (P_{A_{O₂}}), arterial O₂ pressure (P_{a_{O₂}}) and mean pulmonary arterial pressure ($\overline{P}_{ap}$) were measured before gas infusion (control data) and 15 min after starting gas infusion when a steady state phase was reached (infusion data).

TABLE 2b

Effects of infusion of various gases on pulmonary carbon dioxide exchange during constant artificial ventilation.

Gas infusion	(a-A)D _{CO₂} mmHg		P _{a_{CO₂}} infusion	P _{a_{CO₂}} infusion	P _{ap} Infusion
	control	infusion	P _{a_{CO₂}} control	P _{a_{CO₂}} control	P _{ap} control
3.2 ml min ⁻¹ O ₂ N=22	35.3-28.2=7.1 S.E.=1.3	44.1-23.8=20.3 S.E.=0.9	1.250 S.E.=0.022	0.846 S.E.=0.014	1.477 S.E.=0.076
3.2 ml min ⁻¹ He N=11	33.7-27.3=6.4 S.E.=1.0	41.5-22.9=18.6 S.E.=1.2	1.232 S.E.=0.027	0.838 S.E.=0.017	1.584 S.E.=0.051
3.2 ml min ⁻¹ Ne N=14	36.8-32.4=4.4 S.E.=0.9	48.0-24.3=23.7 S.E.=1.3	1.304 S.E.=0.023	0.749 S.E.=0.012	1.951 S.E.=0.037
2.4 ml min ⁻¹ Ne N=13	34.9-31.2=3.7 S.E.=0.8	44.2-25.8=18.4 S.E.=1.9	1.266 S.E.=0.025	0.827 S.E.=0.018	1.739 S.E.=0.031

Arterio-alveolar CO₂ difference [(a-A)D_{CO₂}], arterial CO₂ pressure (P_{a_{CO₂}}), alveolar CO₂ pressure (P_{A_{CO₂}}) and mean pulmonary arterial pressure ($\overline{P}_{ap}$) were measured before gas infusion (control data) and 15 min after starting gas infusion when a steady state phase was reached (infusion data).

Fig. 3

Effects of venous infusion of 3.2 ml min⁻¹ O₂ on the alveolar-arterial pressure differences of O₂ and CO₂ during constant artificial ventilation. All variables were recorded continuously with the exception of PaCO₂.

Fig. 4

Effects of venous infusion of 3.2 ml min⁻¹ air on the alveolar-arterial pressure differences of O₂ and CO₂ during constant artificial ventilation. All variables were recorded continuously with the exception of PaCO₂.

Fig. 5

Recording of several circulatory and respiratory variables during the steady-state phase of $3.2 \text{ ml min}^{-1} \text{ O}_2$ infusion. (Note that the response time of the oxygen electrode is about 0.7 s shorter than that of the CO_2 analyzer).

2. After venous gas injection.

Fig. 6 shows the decrease of P_{aO_2} after injection of various air volumes. Artificial ventilation with a mixture of 60% O_2 and 40% N_2 is used to keep the chemically bound O_2 fraction in the blood constant. During acute massive gaseous lung embolism the decrease of P_{aO_2} depends on the degree of embolization. Fig. 7 shows the relationship between P_{aO_2} and F_{ACO_2} and the intravenous injection of the same volume of various gases. The marked similarity of the curves suggests that injection of these gases causes the same degree of embolization. This is in agreement with the results from a previous investigation concerning the circulatory changes after venous gas injection (see chapter I).

C. Influence of breathing frequency and tidal volume during venous gas infusion on circulatory and respiratory variables.

In Table 3 the results from a representative experiment are listed. During gas infusion ($3.2 \text{ ml min}^{-1} O_2$) ventilation is changed by an increase in tidal volume or by an increase in breathing frequency. The data were obtained in steady state. The circulatory variables are hardly affected by the changed ventilation. The most marked change is a decrease of P_{aCO_2} due to a decreased P_{ACO_2} during hyperventilation. However, the corresponding increase of P_{AO_2} barely affects P_{aO_2} .

Fig. 6

Effect of venous air injection of different volumes on PaO_2 . A gas mixture of 60% O_2 and 40% N_2 was administered in order to keep the oxygen saturation in the blood at 100%. The measurements were done in the end-expiratory part of a respiratory cycle (constant artificial ventilation).

TABLE 3

Effects of changing ventilation during infusion of $3.2 \text{ ml min}^{-1} \text{ O}_2$ on circulation and on pulmonary gas exchange.

Breath. freq. x tidal volume	$P_{\text{A}\text{O}_2}$ mmHg	$P_{\text{A}\text{O}_2}$ mmHg	$P_{\text{A}\text{O}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$P_{\text{A}\text{CO}_2}$ mmHg	$\dot{Q}$ l min ⁻¹
16 x 400 ml	125	69	45	22	40	44	23/12	175/135	3.3	
16 x 550 ml	131	67.5	39	17	33	39	23/12	170/135	3.0	
16 x 400 ml	126	70	42.5	21	39	45	23/12	175/135	3.4	
25 x 400 ml	132	72	39	16	33	38.5	22/12	170/130	3.3	
16 x 400 ml	126	71	43	22	40	46	23/12	175/135	3.2	

alveolar carbon dioxide fraction (%)

Fig. 7

Effect of venous injection of various gases on F_{ACO_2} and $P_{\text{A}\text{O}_2}$. A mixture of 60% O_2 and 40% N_2 was inhaled in order to keep oxygen saturation in the blood at 100%. The measurements of $P_{\text{A}\text{O}_2}$ were done in the end-expiratory part of a respiratory cycle (constant artificial ventilation).

DISCUSSION

For a systemic analysis this discussion is divided into two parts:

- A. changes in ventilation
- B. changes in pulmonary gas exchange

A..All investigations report rapid shallow breathing as a symptom of lung embolism. Bernthal et al. (1961), using glass beads of 75 μ m diameter, found a linear relationship between the amount of emboli and the increase of breathing frequency. They calculated that a minimum obstruction of 10% of the pulmonary circulation was required for tachypnea. Horres and Bernthal (1961) found that the tachpneic response was independent of the localization of the emboli and of their spread in the lung lobe. Cate et al. (1953) and Marazzini et al. (1966) obtained similar results and furthermore found a relationship between the increase in P_{ap} and that in breathing frequency. These results with compact emboli agree with the results from the present investigation using gaseous emboli. In the period between the administration of the emboli and the tachypnea an apneic phase occurred (Niden and Aviado, 1956; Megibow et al., 1942). Afferent neurons in the vagal nerve are important for the causation of the tachypnea during venous embolism, since it immediately disappears after cutting both vagal nerves (Megibow et al., 1942; Hirose et al., 1973). Stimulation of the so-called irritant receptors in the lungs is supposed to be the cause of the tachypneic reflex (Mills et al., 1969), but the mechanism of this stimulation is not certain yet. Mechanical stimulation by the emboli and chemical stimulation by liberated bioamines (serotonin, histamine) have been considered. Megibow et al. (1942) did not find a relationship between the degree of hypoxemia, hypercapnemia and acidosis, and the tachypneic response during pulmonary

embolism caused by starch granules. But in our experiment with CO_2 injection (Fig. 1), assuming that the increased P_{ACO_2} reflects an increased Pa_{CO_2} , it seems that an increased Pa_{CO_2} is also responsible for the ventilatory response.

B. The changes in pulmonary gas exchange depend on the degree of embolization. The alveolar-arterial pressure differences of O_2 and CO_2 increase both by an increase of P_{AO_2} and a decrease of P_{aO_2} and by an increase of P_{ACO_2} and a decrease of P_{aCO_2} , respectively. Arterial hypoxemia is an often mentioned symptom of lung embolism (Behnke et al., 1935/1936; Caldini, 1965; Dick, 1939; Goodwin and Harmel, 1949; Gootman et al., 1962; Khan et al., 1972; Levy et al., 1963; Niden and Aviado, 1956; Sasahara et al., 1967; Williams, 1956; Wolffe and Robertson, 1935). Around 1900 it was expected that intravenous infusion of O_2 might be an important remedy against hypoxemia in patients with chronic lung disease. However, Tunnricliffe reported in 1916 that intravenous infusion of O_2 (600 to 1200 ml h^{-1}) caused cyanosis (referred to by Bond, 1969). In other words the embolic effect of O_2 bubbles predominates over a possible contribution to the oxygenation of the blood. There has been much speculation concerning the origin of arterial hypoxemia during pulmonary embolism. 1. Arterio-venous anastomoses in the pulmonary circulation might be an important factor (Niden and Aviado, 1956), but even the existence of such communications in dog and man is doubtful. 2. A second factor might be a decrease in diffusing capacity. However, Levy et al. (1963) showed that this is a minor factor only. 3. The increased velocity of the blood stream through the open capillaries (Josephson, 1970) also seems to be unimportant, because a contact time of 0.2 - 0.3 s (normally 0.8 s) is still sufficient in normoxia to oxygenate the blood completely (Hlastala, 1973). 4. Alveolar hypoventilation caused by the tachypnea may be ruled out since in the present investigation it is shown that hypoxemia persists even when ventilation is kept constant. 5. A last possibility is a more uneven distribution of the ventilation-perfusion ratio. An

important argument in favor of this factor is the disappearance of arterial hypoxemia when breathing hyperoxic gas mixtures (Gootman et al., 1962; Steffey et al., 1974; Williams, 1956), or when breathing with increased expiratory pressure (Caldini, 1965; Gootman et al., 1962). In the first case the increase of P_{O_2} in all aerated alveoli explains the increased oxygenation of the blood, and in the second case the aerated alveoli which participate in pulmonary gas exchange are increased. Levy and Simmons (1974) and Severinghaus et al. (1961) showed that there is a gas flow shift to the perfused parts of the lungs, but this shift is not sufficient to completely restore the original distribution of ventilation and perfusion. Most investigators used solid particles (glass beads, thrombi, barium sulfate, etc.) as embolic material. One may assume that these emboli are trapped at the same place (at least during the first hours). In this stationary situation the original distribution of ventilation and perfusion may be partly re-established. During venous gas infusion, however, this does not hold because bubbles continually arrive and disappear at different places (see chapter I), so that the distribution of ventilation and perfusion must change from moment to moment. The irregularities in end-expiratory CO_2 and O_2 concentration might reflect this change in the distribution of ventilation and perfusion (Fig. 5; see also Fowler, 1966). During the steady-state phase of gas infusion this does not exclude the presence of a constant overall ventilation-perfusion ratio, as evidenced by constant alveolar-arterial pressure differences of CO_2 and O_2 .

Increase of alveolar ventilation either by increase of breathing frequency or by increase of tidal volume, has no effect on the circulatory steady state during pulmonary gas embolism. This is in agreement with the conclusion from a previous investigation (see chapter I) that the disappearance of the bubbles depends on P_{ap} and the physical properties of the infused gas, but

not on ventilation. However, the gas exchange is affected by an increase of alveolar ventilation during venous gas infusion. P_{aCO_2} decreases parallel to P_{ACO_2} so that the arterio-alveolar CO_2 pressure difference is maintained. P_{aO_2} , however, barely rises with increased P_{AO_2} . A possible explanation for this difference may be derived from the shape of the dissociation curve of these gases. With increasing ventilation in the well ventilated alveoli more CO_2 will be washed out from the blood but only little more O_2 will be taken up by the blood since the hemoglobin is almost saturated with O_2 already. After mixing of this blood with that from poorly ventilated alveoli mean P_{aCO_2} will be decreased but mean P_{aO_2} will not be increased much because 1) the O_2 extra dissolved due to the increased P_{AO_2} is mopped up by the unsaturated blood from the poorly ventilated alveoli, and 2) the decreased P_{aCO_2} and increased pH shift the O_2 dissociation curve to the left.

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CHAPTER III.

EXCRETION OF VENOUS GAS BUBBLES BY THE LUNG

SUMMARY

Intravenous administration of gas bubbles causes acute pulmonary embolism. Increase of pulmonary arterial pressure (P_{ap}), arterial hypoxemia and tachypnea are the most conspicuous changes in circulation and respiration. After stopping the gas administration the circulatory and respiratory values return to their original levels within 10 to 20 minutes. This recovery can be explained by a gradual disappearance of the bubbles from the pulmonary circulation. One of the possible ways is the excretion of gas from the intravascular bubbles into the alveolar air. This can be demonstrated by the appearance of the embolization gas in the expiratory air. To show this, neon has been used since its concentration in ambient air is low (0.018%) and it can be detected by gas chromatography with sufficient accuracy. It could indeed be proven that neon administered intravenously was completely excreted in the lungs and that its excretion curve was closely related to the changes in pulmonary arterial pressure. Alteration of ventilation did not affect the neon wash-out. Increasing P_{ap} due to increasing resistance in the pulmonary circulation by the obstructing bubbles accelerates the bubble excretion. So during venous gas infusion an equilibrium develops between bubble supply and bubble removal, the latter being mainly due to the increased P_{ap} . The limit of this process is determined by the performance of the right ventricle in maintaining its output at increased pulmonary resistance. This conclusion equally applies to any other gas.

Key words: gas embolism - pulmonary embolism - neon detection.

INTRODUCTION

Pulmonary embolism is an affection from which full recovery is possible. Therefore the emboli must be able to disappear from the pulmonary circulation. The way of disappearance depends on the material and size of the emboli. Passage of deformable emboli (fat globules, gas bubbles) through pulmonary capillaries is possible. The occurrence of fat emboli with a diameter of 7 to 35 μm in brain and kidney after venous injection supports this view (Molenaar, 1967; Szabo, 1971). The existence of larger communications around the capillary system in the pulmonary circulation as a possible way of passage for venous emboli is still controversial. Anatomical studies in man and dog demonstrated only one communication from the pulmonary arterial to the pulmonary venous system: the arterio-arterial broncho-pulmonary anastomoses ("Sperr" arteries) which via a T-communication connect with the pulmonary venous system (von Hayek, 1942, 1960; Lauwerijns, 1962; Weibel, 1959). Although there is no generally accepted opinion about the pulmonary passage of large emboli, it is evident that emboli are trapped in the pulmonary circulation. The destiny of these trapped emboli is determined by their material composition: non-metabolizing particles (glass beads, carbon particles etc.) have been found extra-vascularly after one month (Knisely, 1969); blood clots are absorbed completely; fat globules are broken down by lipase. Gas bubbles, however, show an exceptional behavior since their embolic symptoms disappear within half an hour after terminating venous gas administration (see chapter I and II). Two mechanisms may be considered for this fast disappearance of gas bubbles from the pulmonary circulation:

- 1) dissolution of gas molecules in blood and adjacent tissue;
- 2) excretion of gas molecules into the alveolar space.

For gases of high solubility, like CO_2 , the first mechanism will be important. This may be concluded from the finding that CO_2 has a

very small embolizing effect compared with O_2 , He, Ne and N_2 (Spencer and Oyama, 1971; see chapter I and II). To demonstrate the second mechanism Mandelbaum and King (1963) intravenously injected air in dogs breathing oxygen. In the expiratory gas they searched for N_2 with a nitrogen analyzer but found no nitrogen. However, their nitrogen analyzer was too insensitive to detect such small quantities of N_2 . The purpose of the present study was to demonstrate bubble excretion in the lungs using neon which can be detected accurately by gas chromatography.

METHODS

Anesthetized mongrel dogs of either sex, weighing 15 to 25 kg were used. For a description of the anesthesia and of the technical procedure to measure pulmonary arterial, right ventricular and aortic pressure and to apply artificial ventilation the reader is referred to chapter I. Neon was infused intravenously at various rates during 20 min. Expiratory gas was collected in a bag during one minute and analyzed for volume and neon concentration. The samples were taken during the period of infusion in the 1st, 2nd, 3rd, 4th, 5th, 10th, 15th, and 20th min, and after stopping the infusion in the 1st, 2nd, 3rd, 4th, and 5th min. The neon fraction was measured by a gas chromatograph (Permalyzer 350V, Becker) and the gas volume by a spirometer. When neon was injected (20 to 60 ml) samples were taken from end-expiratory air and again analyzed for neon.

RESULTS

From previous investigations it is known that venous gas infusion induces circulatory changes. During infusion at low rates (1 to 5 ml min^{-1}), pulmonary arterial pressure (P_{ap}) increased gradually to a certain level within 10 to 15 min. Continued infusion did not affect P_{ap} any more. After stopping the gas infusion P_{ap} gradually returned to its original level in about 10 to 20 min. Systemic arterial pressure (P_a) and cardiac output ($\dot{Q}$) were hardly affected during low-rate infusions. If the rate of infusion was high P_{ap} increased to a very high level, and the performance of the right ventricle became insufficient as could be seen from a fall of $\dot{Q}$, P_{ap} and P_a (see chapter I).

In Table 1 the data of neon excretion during neon infusion are shown when circulation was in a steady state (18th min after start). In this phase the infused quantity of neon agrees with the expired quantity.

The course of respiratory neon excretion during and after neon infusion in the presence of various ventilatory patterns (several combinations of frequency times tidal volume) is shown in Fig. 1. During the first minutes of the infusion the excreted quantity lags behind the infused quantity; between the 10th and 20th min of the infusion both are about equal; after stopping the infusion the neon infused during the preceding minutes is eliminated. There is no clear effect of the ventilatory pattern on the neon wash-out. The time sequence of the various ventilatory patterns was from top to bottom.

An example of neon wash-out curve with transitory right ventricular insufficiency during infusion is shown in Fig. 2. Between the 15th and 18th min there is a fall in systolic right ventricular pressure ($P_{rv_{syst}}$) accompanied by a fall in mean systemic arterial pressure. No measurements of neon excretion were done in that period. However, since in the subsequent period the excreted quantity of neon

exceeded the infused quantity, even after stopping the infusion, there can be no doubt that in the period of decreased $P_{rv_{syst}}$ the neon wash-out must have been decreased.

That the rate of wash-out of the infused gas must be related to right ventricular performance and mean pulmonary arterial pressure may be seen from Fig. 3. This figure shows the relationship between respiratory neon excretion and diastolic pulmonary arterial pressure after intravenous injection of 20, 40, and 60 ml neon. The similarity of the pressure and excretion curve suggests that they are related.

TABLE 1

Recovery of neon from the lungs: relationship between the quantity of infused and exhaled neon.

Number of experiments	Infused neon ml min ⁻¹	Exhaled neon ml min ⁻¹
7	1.2	1.20 S.E. = 0.09
14	1.6	1.61 S.E. = 0.27
39	2.4	2.31 S.E. = 0.28
16	3.2	3.46 S.E. = 0.32
4	6.0	5.99 S.E. = 0.44

Infusion time was 20 min. Measurements were done at room temperature in the 18th min when pulmonary arterial pressure had reached a constant level. Artificial ventilation was kept constant during the infusion.

Fig. 1.

Excretion curves of neon in expiratory air during and after intravenous infusion of 2.4 ml min^{-1} neon at various rates and depths of artificial ventilation. The sequence of the experiments is, as given in the inset, from top to bottom.

Fig. 2.

Neon excretion in expiratory air ($\dot{V}_{E_{neon}}$) during and after intravenous infusion of 2.4 ml min⁻¹ neon in relation to circulatory changes. Though $\dot{V}_{E_{neon}}$ was not measured during the fall in systolic right ventricular and mean systemic arterial pressure a relationship is suggested between $\dot{V}_{E_{neon}}$ and the circulatory variables.

Fig. 3. $\square$ neon injection

Curves of diastolic pulmonary arterial pressure ($P_{apdiast}$; top) and of alveolar neon fractional concentration ($F_{A_{neon}}$; bottom) after intravenous injection of 20, 40 and 60 ml of neon.

DISCUSSION

A short review of the literature concerning pulmonary passage of large emboli is relevant before discussing the results. A study often referred to in the literature due to its convincing results is that of Prinzmetal et al. (1948). They injected glass spheres varying in diameter between 10 and 440 μm into the venous system of rabbits, cats and dogs. The animals were sacrificed 30 s later, and the liver was digested with hot 30% alcoholic potassium hydroxide to collect the spheres. The diameter of the largest spheres detected varied between 100 and 390 μm . Intracardiac right-to-left communications, the possibility of retrograde flow, and the kind of blood vessels in which the spheres were found were not discussed. Niden and Aviado (1956) found that glass spheres with a diameter of 420 μm passed the pulmonary circulation during artificial perfusion of lung lobes in dogs. The number of the glass spheres passing showed a positive relationship with the perfusion pressure. Tobin (1966) demonstrated passage of glass spheres with a diameter of 200 μm in a similar experiment with human lungs. Contrary to these findings Cate et al. (1953), Fouché et al. (1966), and Ring (1961) could not find any lung passage of solid particles during in vivo experiments. Part of these contradictory findings could be explained by the demonstration of venous reflux of injected venous emboli (Byrne et al., 1953; Daley et al., 1951). Knisely et al. (1956) repeated the experiments of Prinzmetal et al. (1948) and confirmed the presence of emboli (diameter 10 to 2500 μm) in liver and kidney after intravenous injection from various sites; only few beads were found elsewhere. However, when the thoracic inferior vena cava was cut and its venous return was bypassed in order to prevent any possible reflux from the right atrium, no emboli could be demonstrated in liver and kidney. Thus the emboli must have reached the liver not via the arterial circulation (after passage of the pulmonary circulation) but retrogradely via the venous

circulation. The findings of Niden and Aviado (1956) and of Tobin (1966), however, cannot be explained in this way. The only pathway of lung passage in their experiments might have been via the "Sperr" arteries. The high pulmonary arterial perfusion pressure and the absence of any increase of systemic arterial pressure in the bronchial system argue for this pathway.

The second part of this review is devoted to the lung passage of gas bubbles. Mandelbaum and King (1963) reported that they macroscopically saw bubbles in the lung veins in 3 out of 5 experimental animals (dogs) 10 to 30 min after venous injection of $1.5 \text{ ml kg}^{-1} \text{ N}_2$. Deal et al. (1971) placed a bubble trap in the brachiocephalic trunk in 4 sheep to investigate bubble passage through the lungs. In two animals no bubbles, in the third 2 ml, and in the fourth 30 ml were found after venous injection of 60 ml of air; the last animal, however, had an open foramen ovale. Durant et al. (1954), Emerson et al. (1967), Harvey et al. (1944), Marchand and Van Hasselt (1964), Richardson et al. (1937), and Wolffe and Robertson (1935) failed to demonstrate any bubbles in the arterial system after venous administration. A recent method to trace bubbles in blood vessels is the Doppler ultrasonic detection. Spencer and Oyama (1971) intravenously injected every minute CO_2 , O_2 , and N_2 at rates of 0.03, 0.09, and $0.15 \text{ ml kg}^{-1} \text{ min}^{-1}$ in unanesthetized sheep. The detector placed in the brachiocephalic artery only in some cases registered passage of bubbles when at least 100 to 150 ml N_2 had been administered at a rate of $0.15 \text{ ml kg}^{-1} \text{ min}^{-1}$. During CO_2 administration no bubbles could be detected and during O_2 only once. No information was provided concerning bubble size and no symptoms of arterial embolism were reported. Post-mortem examination excluded right-to-left shunts. However, in a similar experiment with anesthetized dogs Steffey et al. (1974) failed to demonstrate any passing bubbles. A third method to study pulmonary passage of bubbles is visualizing the possible passage itself. In 1939 E. and A. Curtillet demonstrated during *in vivo* microscopy that bubbles were arrested in pulmonary arterioles

with a diameter of 30 to 40 μm . Their spherical shape was transformed into a gas column with a length of 200 to 300 μm . From this position the gas was completely absorbed within 5 to 30 min. The conclusion was that bubbles never penetrate into pulmonary capillaries. Knisely et al. (1969) confirmed these findings. Sometimes they saw capillary passage of small bubbles but these were already very small at their arrival. A further less valid method to demonstrate pulmonary passage of bubbles is the presence or absence of symptoms of arterial embolism after daily repeated venous gas injection during several months. Boerema (1962), Gilbert et al. (1968), and Wright (1962) found no signs of arterial embolism after repeated injection of various amounts of air, oxygen or helium in rabbits and dogs.

Most of the reviewed studies in vivo argue for the absence of functional arterio-venous communications in the pulmonary circulation through which venous emboli might pass. The theoretical path via the "Sperr" arteries does not appear to be involved. The pressure gradient from bronchial artery to pulmonary artery does not make it very likely either. The functional significance of the "Sperr" arteries might be the perfusion of atelectatic lung areas with arterial blood (von Hayek, 1954). This is supported by findings in pathological conditions when part of the pulmonary circulation is obstructed. Then one observes an increased perfusion of these arterio-arterial broncho-pulmonary anastomoses (Edwards, 1957; Liebow et al., 1950). However, nothing is really known about the mechanism regulating contraction or relaxation of the "Sperr" arteries.

In this study the question of the fate of venous gas bubbles seems to have been answered. The bubbles trapped in the pulmonary circulation are excreted into the alveolar space. The rate of excretion depends on the pulmonary arterial pressure (P_{ap}). A rise in P_{ap} augments the gas pressure in the bubbles and thus accelerates the net outward movement of gas molecules from the bubbles into the alveolar gas. Then the infused gas will leave the body by alveolar ventilation.

P_{ap} is determined by the output of the right ventricle ($\dot{Q}$) and the resistance of the pulmonary circulation (R_{pc}). R_{pc} is dependent upon the mechanical blockage due to the trapped gas bubbles (and perhaps on an accompanying vasoreaction). When the right ventricle is able to maintain its output a circulatory steady state is reached as the bubble supply by the infusion is in equilibrium with the bubble removal promoted by the increased P_{ap} . The synchronous relationship between the quantity of neon excretion and the increase of P_{ap} is a strong argument for this view, as is the relative independence of neon excretion of the ventilatory pattern. In a previous investigation using different gases (CO_2 , O_2 , N_2 , He, Ne) a relationship could indeed be demonstrated between the increase of P_{ap} and the physical properties of the infused gas (see chapter I). Thus if two different gases are infused intravenously at the same rate, the gas with the higher Krogh diffusion coefficient needs a lower P_{ap} to be excreted at the same rate than that with a low Krogh diffusion coefficient.

When various gases are injected with the same volume then the acute obstruction in the pulmonary circulation will determine R_{pc} and so P_{ap} . The rise in P_{ap} will be practically the same for all gases. However, the rate of bubble excretion and consequently the decrease of P_{ap} will be faster for gases with a higher Krogh diffusion coefficient.

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CHAPTER IV

ORIGIN OF ARTERIAL HYPOXEMIA DURING PULMONARY GAS EMBOLISM

SUMMARY

The purpose of this investigation was to find an explanation for the arterial hypoxemia which occurs during pulmonary gas embolism in normoxic condition. Infusion of oxygen at a rate of 3.2 ml min^{-1} during constant artificial ventilation led to an increase of the normoxic shunt percentage from 2.9 to 21.8. When excluding the contribution of lung units with low ventilation-perfusion ratios to the total shunt by breathing hyperoxic gas mixtures the remaining hyperoxic shunt percentage increased from 2.9 to only 4.3 during inhalation of pure oxygen. There was a linear relationship between the amount of this hyperoxic shunt percentage and the degree of pulmonary gas embolization as expressed by the ratio of diastolic pulmonary arterial pressure during and without embolization. A comparison of the normoxic and hyperoxic increases of shunt percentage due to pulmonary gas embolism suggests that a major part of the arterial hypoxemia in normoxic condition is caused by a marked increase of lung units with low ventilation-perfusion ratios, i.e., by an enhanced unevenness of the distribution of the ventilation-perfusion ratio in the lungs. A moderate increase of the physiological dead space indicates some increase of lung units with high ventilation-perfusion ratios or of the alveolar dead space. The minor increase of the hyperoxic shunt percentage, expressing venous admixture by anatomical veno-arterial and possible atelectatic shunting, is probably due to atelectatic areas in the lungs. CO_2 elimination during the same extent of pulmonary gas embolization was more impaired during hyperoxia than during normoxia. This effect may be due to the release of hypoxic vasoconstriction in lung units with low ventilation-perfusion ratios by hyperoxia, leading to an extra shift of blood to these lung units and to impaired CO_2 elimination because the CO_2 pressure gradient is too small to compensate for the low ventilation in these lung units.

Key words: gas embolism - pulmonary embolism - ventilation-perfusion ratio - atelectasis

INTRODUCTION

In previous investigations it was found that venous gas infusion at low rates (1 to 5 ml min^{-1}) causes arterial hypoxemia in the presence of unaltered cardiac output and (artificial) ventilation (see chapter I and II). This hypoxemia might be due to venous admixture by four theoretically possible mechanisms of shunting:

1. Direct arterio-venous anastomoses from the pulmonary artery to the pulmonary veins;
2. Venous admixture through anatomical channels from the bronchial venous circulation into the pulmonary venous system and from the Thebesian and mediastinal veins into the left atrial or ventricular cavity;
3. Venous blood from pulmonary arterial-bronchial arterial anastomoses ("Sperr" arteries; diameter $50 - 400 \mu\text{m}$) ahead of the respective capillary beds, streaming from the pulmonary arterial into the pulmonary venous system through a T-connection from the "Sperr" arteries to the plexus venosus peribronchialis which feeds into the pulmonary veins (by veno-venous broncho-pulmonary anastomoses) (von Hayek, 1942, 1960; Lauwerijns, 1962; Molenaar, 1967).
4. Venous admixture from pulmonary capillaries of lung units with low ventilation-perfusion ratios; if the ventilation-perfusion ratio becomes zero (atelectasis) this venous admixture behaves like an anatomical veno-arterial shunting with the exception that it is reversible, contrary to the anatomical channels.

When investigating the possible significance of these mechanisms for the arterial hypoxemia during venous gas infusion three of them can be ruled out a priori. Anatomical studies have failed to demonstrate any pulmonary arterio-venous anastomoses in man and dog. In the "Sperr" arteries the direction of flow is from the bronchial to the pulmonary

artery due to the physiological pressure conditions; a venous admixture through these connections would only be possible if the direction of flow would be reversed due to a reversal of the pressure gradients. The observation that pulmonary arterial pressure was always far below systemic arterial pressure in all our venous gas infusion experiments argues against a possible contribution to venous admixture from this source; it must be admitted, however, that the local pressure conditions at the sites of pulmonary vascular obstruction remain unknown and therefore a possible, probably minor, venous admixture by this mechanism cannot be excluded completely. A further argument against an important contribution from this pathway is the fact that venous gas bubbles are completely excreted into the alveolar air (see chapter III) although this again does not entirely preclude any possible involvement of the "Sperr" arteries within the limits of experimental error. Venous admixture by other anatomical channels as mentioned under 2 above had been estimated to correspond to a few percent of total blood flow in the dog (Schuurmans Stekhoven and Kreuzer, 1967). There is no reason to presume that this shunt percentage should be altered appreciably during venous gas infusion under the present experimental conditions. It may be concluded by exclusion, therefore, that intrapulmonary venous admixture should be the most important contribution to explain arterial hypoxemia during venous gas infusion.

As mentioned above, however, we will have to distinguish between venous admixture from lung units with a low ventilation-perfusion ratio and that from lung units with a ventilation-perfusion ratio of zero, i.e., atelectasis. The physiological shunt calculated during air breathing is composed of intrapulmonary venous admixture from pulmonary capillaries in lung areas with low or zero values of the ventilation-perfusion ratio as well as extrapulmonary anatomical venous admixture from all possible sources mentioned above. In the ideal lung the physiological shunt would equal the anatomical shunt. Application of hyperoxia will exclude the contribution from lung units with low ventilation-perfusion ratios (since the high pressure gradient of oxygen

increases the oxygen pressure in the hypoventilated lung units too), but not that from atelectatic lung areas which behave similarly to venous admixture through anatomical veno-arterial shunting and may become more prominent when breathing pure oxygen, nor that from extrapulmonary anatomical shunting. If we neglect all other factors (1 to 3) or their changes as explained above, any changes of shunt percentage calculated during normoxia or hyperoxia occurring during venous gas infusion will therefore have to be interpreted predominantly in terms of the intrapulmonary venous admixture of both kinds, i.e. due to low or to zero ventilation-perfusion ratios.

It is the purpose of the present paper to elucidate the origin of arterial hypoxemia during pulmonary gas embolism in normoxic condition.

METHODS

Anesthetized mongrel dogs of either sex, weighing 15 to 25 kg, were used. For a description of the anesthesia and of the procedure to measure pulmonary arterial and aortic pressure, blood and alveolar gas pressures and to apply artificial ventilation the reader is referred to chapter I and II.

Total pulmonary shunt at normoxia was calculated from the formula:

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{C_{c'O_2} - C_{aO_2}}{C_{c'O_2} - C_{\bar{v}O_2}} \times 100\%$$

where $\dot{Q}_s$ = shunt flow

$\dot{Q}_t$ = total flow

$C_{c'O_2}$ = end-capillary oxygen concentration in ml l⁻¹

C_{aO_2} = arterial oxygen concentration in ml l⁻¹

$C_{\bar{v}O_2}$ = mixed venous oxygen concentration in ml l⁻¹

To exclude the contribution of lung units with low ventilation-

perfusion ratios to the shunt flow hyperoxic gas mixtures were used. When the Hb of the arterial blood is completely oxygenated the following formula may be used to calculate the hyperoxic shunt:

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{\alpha(P_{A_{O_2}} - P_{a_{O_2}})}{\alpha(P_{A_{O_2}} - P_{a_{O_2}}) + C_{a_{O_2}} - C_{\bar{v}_{O_2}}} \times 100\%$$

where α = solubility coefficient of oxygen in ml ml⁻¹ mmHg⁻¹

$P_{A_{O_2}}$ = alveolar oxygen pressure in mmHg

$P_{a_{O_2}}$ = arterial oxygen pressure in mmHg

This shunt percentage includes anatomical veno-arterial shunting (irreversible) and atelectatic venous admixture (reversible) (Schoor-
mans Stekhoven and Kreuzer, 1967).

Physiological dead space was calculated from the formula:

$$V_{D_{\text{physiol}}} = \frac{P_{a_{CO_2}} - P_{E_{CO_2}}}{P_{a_{CO_2}}} \times V_T$$

where $V_{D_{\text{physiol}}}$ = physiological dead space in ml

$P_{a_{CO_2}}$ = arterial carbon dioxide pressure in mmHg

$P_{E_{CO_2}}$ = mixed expiratory carbon dioxide pressure in mmHg

V_T = expiratory tidal volume in ml

All these calculations were made during and without venous gas infusion.

RESULTS

It is known from previous investigations that venous gas infusion increases pulmonary arterial pressure (P_{ap}). This increase of P_{ap} depends on the physical properties of the infused gases and on the rate of infusion. If the increase of P_{ap} does not impair right ventricular

performance to maintain its output, P_{ap} reaches a steady level after 10 to 15 min. The increase of P_{ap} then is a measure of the resistance of the pulmonary circulation and thus of the degree of embolization. As shown in Fig. 1 there exists a linear relationship between the calculated shunt percentage in hyperoxic condition and the ratio of diastolic P_{ap} as measured during venous gas infusion after reaching a constant level and before venous gas infusion ($r = 0.973$). Shunt percentage without gas infusion normally is 1% to 3% at hyperoxia in the dog (Schuurman Stekhoven and Kreuzer, 1967). This shunt percentage during venous gas infusion is increased by only 1.5% to 6% (with the exception of one experimental animal with an increase of 10% and 14%). The effects of different hyperoxic mixtures (40%, 60%, 100% O_2) on the circulatory and respiratory variables during and without venous gas infusion are presented in Table 1 for a representative experiment. Systemic arterial pressure (P_a) and cardiac output ($\dot{Q}$) are hardly affected but P_{ap} is about 4 mmHg higher during normoxia than during hyperoxia and about 9 mmHg higher during gas infusion than without gas infusion. Venous gas infusion impairs the gas exchange as seen from the respiratory data. Most marked is a decrease of P_{aO_2} from 103 to 77 mmHg during venous gas infusion at normoxia. During venous gas infusion the shunt percentage increases by about 1.5% for all hyperoxic gas mixtures but by 19% during normoxia. Physiological dead space, however, increases by only 45 to 62 ml.

Another effect of hyperoxic ventilation during venous gas infusion is shown in Table 2. When during a steady-state phase of venous gas infusion and constant ventilation air breathing is changed to oxygen breathing, the arterio-alveolar gradient of CO_2 increases from 21 to 28 mmHg. A change in reverse direction causes an opposite effect. Without venous gas infusion this effect is hardly present. Physiological dead space is increased from 315 to 333 ml. This phenomenon will also be analyzed in the Discussion. In Table 3 the results of a typical gas infusion experiment are listed where the circulation first tends to fail and subsequently recovers again. P_{aCO_2} increases up to 95 mmHg concomitant with an increase of $V_{D_{physiol}}$. Yet oxygenation of the blood

remains adequate during hyperoxic ventilation. The calculated shunt is not higher than 7 and 5% during hyperoxia. These results will be further considered in the Discussion.

Fig. 1

Plot of degree of embolization against shunt percentage at hyperoxia. As a measure of the degree of embolization caused by venous gas infusion the ratio of $P_{ap\ diast}$ as measured during and without embolization is used. There is a correlation with $r = 0.973$ between this ratio and the calculated shunt percentage. When the absolute differences in shunt during and without embolization were compared there was an increase of 1.5 to 6% during embolization. One experimental animal had an increase of shunt during embolization of 10 to 14% (the latter value is beyond the scale of the figure).

Table 1

Effects of venous gas embolism induced by oxygen infusion at a rate of 3.2 ml min^{-1} on respiratory and circulatory variables during constant artificial ventilation ($f = 15 \text{ min}^{-1}$, $V_T = 450 \text{ ml}$) with different oxygen mixtures in a representative experiment.

F_{IO_2} %	20.97		38.37		61.41		99.34	
Time of measurement	control	gas infusion	control	gas infusion	control	gas infusion	control	gas infusion
$\dot{Q} \text{ l min}^{-1}$	3.0	2.8	3.2	2.6	3.2	2.6	2.8	2.6
$P_a \text{ mmHg}$	195/130	185/130	185/140	185/140	185/140	185/140	185/140	185/140
$P_{ap} \text{ mmHg}$	32/14	36/23	27/10	33/19	26/10	33/19	26/10	32/19
$(A-a)D_{O_2} \text{ mmHg}$	14	44	15	55	35	65	40	70
$P_{AO_2} \text{ mmHg}$	117	121	250	255	400	405	675	680
$P_{aO_2} \text{ mmHg}$	103	77	235	200	365	340	635	610
$P_{\dot{V}O_2} \text{ mmHg}$	45	41	60	51	56	52	56	56
$(a-A)D_{CO_2} \text{ mmHg}$	6	16	6	18	6	20	6	20
$P_{ACO_2} \text{ mmHg}$	30	27	30	27	30	27	30	27
$P_{aCO_2} \text{ mmHg}$	36	43	36	45	36	47	36	47
$P_{\dot{V}CO_2} \text{ mmHg}$	43	52	44	58	45	59	46	58
% shunt ($\dot{Q}_s/\dot{Q}_t$)	2.9	21.8	1.2	2.7	2.0	3.6	2.9	4.3
$V_{D\text{physiol}} \text{ ml}$	225	273	225	270	225	287	220	282

Table 2

Effects of hyperoxia on circulatory and respiratory variables during infusion of $3.2 \text{ ml min}^{-1} O_2$ and constant artificial ventilation ($f = 15 \text{ min}^{-1}$, $V_T = 450 \text{ ml}$).

F_{IO_2}	21	100
$\dot{Q} \text{ l min}^{-1}$	3.0 ± 0.5	3.0 ± 0.5
$P_a \text{ mmHg}$	$140/100 \pm 20/20$	$140/100 \pm 20/20$
$P_{ap} \text{ mmHg}$	$23/12 \pm 3/3$	$23/12 \pm 3/3$
$(A-a)D_{O_2} \text{ mmHg}$	45 ± 6	105 ± 20
$P_{AO_2} \text{ mmHg}$	120 ± 5	675 ± 5
$P_{aO_2} \text{ mmHg}$	75 ± 7	570 ± 30
$P_{\dot{V}O_2} \text{ mmHg}$	43 ± 4	60 ± 8
$(a-A)D_{CO_2} \text{ mmHg}$	21 ± 4	28 ± 5
$P_{ACO_2} \text{ mmHg}$	24 ± 4	22 ± 4
$P_{aCO_2} \text{ mmHg}$	45 ± 4	50 ± 6
$P_{\dot{V}CO_2} \text{ mmHg}$	52.5 ± 3	60 ± 3
$V_{D\text{physiol}} \text{ ml}$	315 ± 12	338 ± 15

The data (with standard error) were obtained from 10 experiments during the steady state of oxygen infusion.

Table 3

Values of circulatory and respiratory variables of a typical experiment showing the effects of temporary circulatory failure during venous infusion of 3.2 ml min^{-1} neon at constant artificial ventilation ($f = 15 \text{ min}^{-1}$, $V_T = 450 \text{ ml}$) with gas mixtures of various oxygen fraction.

Time	- 15 min	15 min	30 min	40 min	55 min
Gas mixture	air	air	60% O_2 - 40% N_2	100% O_2	air
$\dot{Q} \text{ l min}^{-1}$	3.0	2.3	2.1	1.4	3.8
$P_a \text{ mmHg}$	165/125	100/65	115/75	90/50	165/100
$P_{aP} \text{ mmHg}$	34/15	33/22	44/32	38/29	60/40
$(A-a)D_{\text{O}_2}$	34	58	180	265	69
$P_{A\text{O}_2} \text{ mmHg}$	116	122	410	680	110
$P_{a\text{O}_2} \text{ mmHg}$	82	64	230	415	41
$P_{v\text{O}_2} \text{ mmHg}$	39	33	53	43	23
$(a-\bar{A})D_{\text{CO}_2} \text{ mmHg}$	5	21	58	80.5	47.5
$P_{A\text{CO}_2} \text{ mmHg}$	31	22	16	14.5	40.5
$P_{a\text{CO}_2} \text{ mmHg}$	36	43	74	95	88
$P_{v\text{CO}_2} \text{ mmHg}$	48.5	56.2	93	115	112
pH_a	7.430	7.352	7.207	7.088	7.108
pH_v	7.383	7.332	7.180	7.060	7.088
% shunt ($\dot{Q}_s/\dot{Q}_t$)	14.3	23.8	7	5	66.5
$V_{D\text{physiol}} \text{ ml}$	189	279	378	378	310

Neon infusion was started at 0 min and the gas mixture was changed immediately after the time of measurement.

DISCUSSION

Pulmonary embolism is commonly accompanied by arterial hypoxemia. When pathological right-to-left shunts are excluded, and cardiac output and (artificial) ventilation remain constant the only shunt responsible for this arterial hypoxemia can be an enhanced venous admixture from lung units with low or zero ventilation-perfusion ratios, possibly due to increased blood flow through these lung regions. Vascular occlusion by the gas emboli on the other hand should lead to an increased alveolar dead space in the lung. In control condition without venous gas infusion the differences in shunt percentage at various levels of oxygenation are only minor. During gas infusion the shunt increases by almost 19% at normoxia but by only 1.5% at hyperoxia (see Table 1). Thus the most important origin of arterial hypoxemia during venous gas infusion must be an increased venous admixture from lung units with low ventilation-perfusion ratios. This may easily be understood by a consideration of the possible distribution of the infused venous gas emboli. The emboli floating in the blood stream will preferably turn to those arterioles where the blood flow is highest. After obstruction of these arterioles the blood has to follow other pathways (possibly favored by increasing pulmonary arterial pressure). Thus the blood flow may increasingly shift to lung units with low ventilation-perfusion ratios and lead to arterial hypoxemia. A confirmation of this mechanism would be the demonstration of a beneficial effect of an improved distribution of alveolar ventilation on arterial hypoxemia. This may be provoked by an increase in end-expiratory pressure. Caldini (1965) and Gootman et al. (1962) indeed found that such an increase in end-expiratory pressure decreased hypoxemia during pulmonary embolism.

After having demonstrated the major shunting factor during pulmonary embolism at normoxia the question rises how the increased shunt at hyperoxia might be explained. It has been mentioned above that the shunt calculated during hyperoxia includes not only anatomical but also atelectatic shunting (Schuurmans Stekhoven and Kreuzer, 1967). Dantzker et al.

(1975) observed the development of shunts during oxygen breathing because lung units with ventilation-perfusion ratios below a critical value are unstable and become atelectatic. Thus the increase of shunt at hyperoxia during pulmonary embolism, when the blood flow is already shifted to lung units with low ventilation-perfusion ratios, might be due to blood flow from atelectatic lung areas. The relationship between the hyperoxic shunt percentage and the pulmonary arterial pressure necessary to overcome the high vascular resistance due to hypoxic vasoconstriction in atelectatic lung areas during venous gas infusion is compatible with this view (see Fig. 1). However, this atelectatic shunting cannot be considerable in view of the rather minor increase in hyperoxic shunt percentage (Table 1).

in hyperoxic shunt percentage (Table 1).

Concerning CO₂ elimination another effect of hyperoxia as compared with normoxia in pulmonary embolism may be demonstrated (Table 2). Without venous gas infusion CO₂ pressures at hyperoxia are the same as at normoxia with the exception of a slightly increased mixed venous CO₂ pressure due to the Haldane effect (Hlastala, 1973; Lenfant, 1966). During venous gas infusion, however, hyperoxia impairs CO₂ elimination as seen from the increased values of $P_{a_tO_2}$ and $(a-A)D_{CO_2}$ as compared with normoxia (Table 2), which are indicative of an increased alveolar and therefore physiological dead space. It is generally accepted that oxygen plays a major role in the regulation of the ventilation-perfusion ratio of lung units (Duke and Lee, 1963; Fishman, 1961; Hales et al., 1975; Levy et al., 1974; Severinghaus et al., 1961; West, 1969). During pulmonary embolism there already is a shift of blood flow to lung units with low ventilation-perfusion ratios as described above. When hypoxic vasoconstriction in such lung units is released by hyperoxic gas mixtures in the presence of unchanged total ventilation, there occurs an extra shift of blood to these lung units. Oxygen uptake by the blood is hardly affected by this phenomenon because alveolar P_{O_2} will rise to hyperoxic levels in all ventilated alveoli, but CO₂ elimination from

the blood will be more impaired because its pressure gradient is too small to compensate for the low ventilation in lung units with low ventilation-perfusion ratios.

Table 3 at last demonstrates the marked changes occurring during venous gas infusion in the presence of failing circulation. In the control phase most variables of this typical experiment were within the physiological range but the increased values of the $(A-a)D_{O_2}$ and of the normoxic shunt percentage concomitant with a decreased P_{aO_2} as compared with the respective values in Table 1 point to a certain impairment of the gas exchange capacity. After starting intravenous neon infusion (3.2 ml min^{-1}) during constant ventilation the circulation became insufficient: $\dot{Q}$ decreased from 3.0 to 2.3 l min^{-1} and P_a from $165/125$ to $100/65 \text{ mmHg}$ but $P_{apdiast}$ increased from 15 to 22 mmHg due to the vascular obstruction by the bubbles. Since heart frequency remained constant the decrease of pulmonary pulse pressure from 19 to 11 mmHg was an expression of a decreased right ventricular stroke volume (the animal was atropinized). The increase of $P_{apdiast}$ was thus the net effect of decreased $\dot{Q}$ and increased vascular resistance (obstruction by neon bubbles). The changes in the gas pressures and the increase of $\dot{Q}_s/\dot{Q}_t$ from 14.3 to 23.8% were caused by a shift of blood flow to lung units with low ventilation-perfusion ratios. 16 min after starting neon infusion the gas mixture was changed from air to $60\% \text{ O}_2$ and $40\% \text{ N}_2$. 14 min later $\dot{Q}$ further decreased to 2.1 l min^{-1} , but P_a was somewhat increased from $100/65$ to $115/75 \text{ mmHg}$ due to vasoconstriction. $P_{apdiast}$ also increased from 22 to 32 mmHg , probably due to further obstruction of the vessels by the infused gas bubbles. Gas exchange showed a remarkable pattern in that oxygenation of the blood was adequate ($P_{aO_2} = 230 \text{ mmHg}$), but CO_2 wash-out from the blood was very seriously impaired ($P_{aCO_2} = 74 \text{ mmHg}$). Shunt percentage was not higher than 7% , while $V_{Dphysiol}$ increased further to 378 ml ($V_T = 450 \text{ ml}$). Again 10 min later, during ventilation with $100\% \text{ O}_2$, circulation was impaired even more and P_{aCO_2} increased to 95 mmHg . When the gas mixture was changed from 100%

O₂ to air, however, circulation recovered immediately: $\dot{Q}$ increased from 1.4 to 3.8 l min⁻¹, P_a from 90/50 to 165/100 mmHg, and P_{ap} from 38/29 to 60/40 mmHg. At the same time V_{Dphysiol} decreased from 378 to 310 ml, and the enormous (a-A)D_{CO₂} decreased from 80.5 to 47.5 mmHg. But with air breathing P_{aO₂} now dropped to 41 mmHg. These data clearly demonstrate that hyperoxia leads to respiratory acidosis during pulmonary gas embolism and that circulatory failure enhances this effect.

Thus treatment with hyperoxic gas mixtures during pulmonary embolism may be risky. Normoxic ventilation during pulmonary embolism on the other hand leads to hypoxemia, though possibly in the presence of an improved circulatory condition (Table 3). Hyperventilation with hyperoxic gas mixture might both increase P_{aO₂} and decrease P_{aCO₂}.

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CHAPTER V

GAS MOVEMENT BETWEEN ALVEOLAR SPACE AND INTRAVASCULAR GAS
BUBBLES IN THE PULMONARY CIRCULATION

SUMMARY

It was found in previous investigations that during venous gas infusion at low rates (1 to 5 ml min⁻¹) circulatory and respiratory variables reached a constant level after about 10' to 15 min. The present study demonstrates that this steady state can be disturbed by changing the composition of the breathing gas mixture. Alteration from air to 21% O₂ in helium rapidly increased the embolic effects up to a maximum within 1.5 to 2 min; in the next 5 to 8 min the circulatory and respiratory variables returned to their previous levels during air breathing. Reverse effects occurred when changing from 21% O₂ in helium to air. Similar phenomena were seen after switching from air to pure oxygen and from 21% O₂ in helium to pure oxygen. However, the extent of the circulatory and respiratory changes differed depending on the composition of the respective alternating breathing gas mixtures and on the initial embolic level as determined by infusion rate and kind of infusion gas.

Gas movements between intravascular bubbles and alveolar space might be responsible for these changes. When the gas in the alveolar space is altered from nitrogen to helium, e.g., a gas flux of helium into the intravascular bubbles will ensue due to its partial pressure difference. On the other hand nitrogen will pass from the bubbles into the alveolar space due to the partial pressure difference too. The rate of these diffusion processes depends on Krogh's diffusion coefficient of both gases. Since Krogh's diffusion coefficient of helium is higher than that of nitrogen a net flux of helium from the alveolar space in the intravascular bubbles will occur as long as the flux equalling the product of pressure difference and Krogh's diffusion coefficient of helium exceeds that of nitrogen. After the two fluxes have become equal a phase of net gas movement

out of the bubbles follows since the pressure difference of nitrogen is still high, while that of helium has declined to zero, and furthermore the gas movement from the bubbles into the alveolar space is favored by the fact that the driving pressure is the difference between the sum of atmospheric and pulmonary arterial pressure in the bubbles and atmospheric pressure in the alveolar space. However, this pressure difference was only 10 to 30 mmHg and thus negligible compared with the partial pressure differences of the gases (500 to 600 mmHg) just after the change of the breathing gas mixture. Therefore in the first minutes after alteration of the breathing gas mixture from air to 21% O₂ in helium the net gas flux of helium into the intravascular bubbles enlarged the bubbles as evidenced by an increase in pulmonary vascular resistance (increase of P_{ap} divided by constant flow), and later a net gas flux of nitrogen out of the bubbles decreased the size of the bubbles as evidenced by a decrease in pulmonary vascular resistance. The same process would take place after switching from air or 21% O₂ in helium to pure oxygen. This phenomenon might be important for the treatment of pulmonary gas embolism, e.g., in decompression sickness.

Key words: pulmonary embolism - gas embolism - decompression sickness - Krogh's diffusion coefficient.

INTRODUCTION

Previous investigations have shown that venous gas infusion at constant artificial ventilation increases pulmonary arterial pressure (P_{ap}) without any change in systemic arterial pressure (P_a) or cardiac output ($\dot{Q}$) (see chapter I), and augments alveolar-arterial O₂ and CO₂ pressure differences ($(A-a)D_{O_2}$ and $(a-A)D_{CO_2}$) (see chapter II). When venous gas infusion leads to moderate em-

bolism only, the circulatory and respiratory changes reach a steady state about 10 to 15 min after starting the infusion. Severe embolism with a high P_{ap} due to massive obstruction of the pulmonary circulation will impair right ventricular function accompanied by a fall in $\dot{Q}$. Two factors determine the extent of embolism during venous gas infusion:

- 1) the rate of infusion and
- 2) Krogh's diffusion coefficient of the gas infused.

It has been demonstrated in another study that infused neon bubbles are excreted by the lungs (see chapter III). In steady state the rate of excretion equals the rate of infusion. The rate of infusion and Krogh's diffusion coefficient determine the amount of increase in P_{ap} when reaching an equilibrium between bubble supply and removal.

These findings led us to study the possible gas movement from alveolar space into intravascular bubbles as influenced by a change of the breathing gas mixtures. When in the alveolar space a gas with a low Krogh diffusion coefficient, e.g., N_2 , is replaced by a gas with a high Krogh diffusion coefficient, e.g., He or O_2 , the total gas movement into the bubbles exceeds the outward movement until a new equilibrium is reached. The bubbles will enlarge and thus increase the resistance in the pulmonary circulation as may be concluded from an increase in P_{ap} . When He or O_2 is replaced by N_2 the reverse process will ensue.

METHODS

For a description of the preparation of the animals and of the measuring procedure of the circulatory and respiratory variables the reader is referred to chapter I and chapter II. In the present study the effect of a change of various breathing gas mixtures (air, 21% O_2 in helium, 100% O_2) during venous gas infusion on circulatory

and respiratory variables is investigated in five dogs. Oxygen, helium and air were used as infusion gases administered at a rate of 3.2 ml min^{-1} . When a steady state in the circulatory and respiratory variables was reached the breathing gas mixture was changed. To exclude the effect of the physical properties of the infusion gases the same procedure was performed with air infusion at various rates. At last the influence of various breathing gas mixtures on the effects of venous gas injection was investigated.

RESULTS

A. Effects of change of breathing gas mixture on diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration during venous infusion of air, helium or oxygen at the same rate.

During the steady state of intravenously induced pulmonary gas embolism where diastolic pulmonary arterial pressure ($\text{Pap}_{\text{diast}}$) and alveolar CO_2 fractional concentration (F_{ACO_2}) had reached constant levels, the breathing gas mixture was changed. Figure 1 shows the changes in $\text{Pap}_{\text{diast}}$ and F_{ACO_2} during infusion of air, helium and oxygen after a change from air to 21% O_2 in helium and vice versa in a typical experiment. When changing from air to 21% O_2 in helium $\text{Pap}_{\text{diast}}$ rapidly increases up to a maximum within 1.5 to 2 min; thereafter $\text{Pap}_{\text{diast}}$ gradually returns to its initial level. The tracings of F_{ACO_2} are synchronous with and in opposite direction to those of $\text{Pap}_{\text{diast}}$. Alteration from 21% O_2 in helium to air induces changes in $\text{Pap}_{\text{diast}}$ and F_{ACO_2} in reverse direction. Similar changes occur when air is replaced by 100% O_2 and vice versa (Fig. 2). However, after switching from 100% O_2 to 21% O_2 in helium and vice versa the extent of changes in $\text{Pap}_{\text{diast}}$ and F_{ACO_2} is clearly smaller (Fig. 3). Furthermore when changing from 21% O_2 in helium to 100% O_2 the decrease in $\text{Pap}_{\text{diast}}$ is not accompanied by an in-

Fig. 1

Effect of change of breathing gas from air to 21% O₂ in helium and vice versa on diastolic pulmonary arterial pressure and alveolar O₂ fractional concentration during venous infusion of air, helium or oxygen at a rate of 3.2 ml min⁻¹. Artificial ventilation was kept constant and systemic arterial pressure did not change.

Fig. 2

Effect of change of breathing gas from air to 100% O₂ and vice versa on diastolic pulmonary arterial pressure and alveolar CO₂ fractional concentration during venous infusion of air, helium or oxygen at a rate of 3.2 ml min⁻¹. Artificial ventilation was kept constant and systemic arterial pressure did not change.

Fig. 3

Effect of change of breathing gas from 100% O₂ to 21% O₂ in helium and vice versa on diastolic pulmonary arterial pressure and alveolar CO₂ fractional concentration during venous infusion of air, helium or oxygen at a rate of 3.2 ml min⁻¹. Artificial ventilation was kept constant and systemic arterial pressure did not change.

crease but rather by a decrease in F_{ACO_2} . When comparing the extent of the changes in $P_{apdiast}$ and F_{ACO_2} with respect to the nature of the infused gases, it will be seen that these responses are most marked during infusion of air, followed in declining order by those during helium and oxygen infusion.

B. Effects of change of breathing gas mixture on diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration during venous infusion of air at different rates.

In order to eliminate the effect of the physical properties of the infused gas on the extent of the changes in $P_{apdiast}$ and F_{ACO_2} (see chapters I and II), air was infused at different rates to produce varying initial control levels of $P_{apdiast}$ and F_{ACO_2} . Fig 4 shows that when changing from air to 21% O_2 in helium and vice versa, the extent of the changes in $P_{apdiast}$ and F_{ACO_2} depends on the initial control levels.

C. Influence of different breathing gas mixtures on the effect of venous injection of 25 ml air on diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration.

Previous investigations have shown that during air breathing venous injection of different gases causes similar changes in $P_{apdiast}$ and F_{ACO_2} (see chapters I and II). Fig 5 shows that the kind of breathing gas affects the changes in $P_{apdiast}$ and F_{ACO_2} after venous injection of 25 ml air. In the first 40 sec after the injection the curves run parallel in agreement with previous findings. Thereafter, however, $P_{apdiast}$ and F_{ACO_2} further increase and decrease respectively for another minute during 21% O_2 in helium or 100% O_2 breathing. Then both curves gradually return to a course parallel to that during air breathing.

Fig. 4

Effect of change of breathing gas from 21% O₂ in helium to air and vice versa on diastolic pulmonary arterial pressure and alveolar CO₂ fractional concentration during venous infusion of air at a rate of 1.6, 2.4 or 3.2 ml min⁻¹. Artificial ventilation was kept constant and systemic arterial pressure did not change.

Fig. 5

Effect of various breathing gases on change of diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration after venous injection of 25 ml air. Artificial ventilation was kept constant and systemic arterial pressure did not change.

DISCUSSION

Several studies have been performed on the behavior of gas bubbles in the body. Piiper (1970) found by theoretical analysis of the absorption of inert gases from gas cavities in the body that a model of equal diffusion resistance for all capillaries effective in gas absorption is most satisfactory. Hlastala and van Liew (1975) mentioned that the time for complete disappearance of inert gas bubbles depends on the initial bubble size, the perfusion rate of the tissue, the physical characteristics of the inert gas, and the expression $(1 - P_a/P_g)$, where P_a and P_g are the inert gas partial pressures in the surrounding tissue and inside the bubble respectively. They calculated the time for the disappearance of a nitrogen bubble of 1 mm radius in an O_2 -breathing man to be 100 - 250 min depending on blood perfusion. Breathing air increases the time of persistence of the bubble about 10 times. Experiments on the absorption of gas bubbles in flowing blood were done by Hlastala and Farhi (1973). The time for a nitrogen bubble of a radius of 2800 μm to decrease to a radius of 500 μm was about 85 min. In this experiment the nitrogen partial pressures in the bubble and in the blood were 657 and 88.5 mmHg respectively. When breathing air the bubble would disappear in 560 min.

Bubbles in the pulmonary circulation disappear within 10 to 20 min as may be deduced from the disappearance of circulatory and respiratory symptoms after venous gas administration (see chapters I and II) and from the excretion of gas from bubbles trapped in the pulmonary circulation (see chapter III). The relatively thin tissue barrier between the intravascular bubble and the alveolar space may be responsible for the fast absorption of these bubbles. The bubbles are arrested in the arterioles where they are elongated into gas columns and absorbed (E. and A. Curtillet, 1939; Knisely, 1957). Even in the systemic circulation bubbles have never been observed to pass from arterioles into capillaries since the blood pressure is not sufficient

to overcome the increase in surface tension of small bubbles (Buckles, 1968).

The purpose of the present study was to demonstrate gas movement from the alveolar space into intravascular gas bubbles in the pulmonary circulation. Jameson (1963) demonstrated diffusion of gases from alveoli to precapillary arteries by detection of hydrogen or oxygen at the tip of a catheter in wedge position in a branch of the pulmonary artery after inhalation of these gases. We studied changes in circulatory and respiratory variables due to increase or decrease of bubble size. Strauss and Kunkle (1974) found in a model in which stable bubbles were created in gelatin by decompression, that switching the contacting gas from N_2 to He caused bubbles to grow, whereas switching from He to N_2 caused bubbles to shrink or disappear. This finding was confirmed for subcutaneous pockets containing various gases in rats (Piiper et al., 1962; Tucker and Tenney, 1966; Van Liew and Passke, 1967). Our results agree with these findings. When N_2 (Krogh's diffusion coefficient = 0.0353×10^{-5}) in the alveolar space is replaced by He (Krogh's diffusion coefficient = 0.0706×10^{-5}) or by O_2 (Krogh's diffusion coefficient = 0.0743×10^{-5}) the intravascular bubbles will grow as indicated by an increase of P_{ap} and a decrease of F_{ACO_2} . Conversely replacing He or O_2 by N_2 elicits the opposite effect. The extent of changes in P_{ap} and F_{ACO_2} due to a change of the breathing gas appears to depend on the degree of embolization, i.e. on the total amount of gas bubbles in the pulmonary circulation. This can be deduced from Results A and B: the higher the initial P_{ap} the larger the change. The limit of the increase or decrease in bubble size is reached when the net inward movement of gas molecules equals their net outward movement (peaks and dips in the curves of Figs. 1 to 4). Concerning the gas movements due to partial pressure differences this equilibrium is reached when the product of pressure difference times Krogh's diffusion coefficient of the inward-moving

gas equals that of the outward-moving gas. After reaching this equilibrium the diffusion of the gas with the lower Krogh diffusion coefficient will then exceed that of the faster gas because its pressure gradient remains high for a longer time. The previous effect of the fast-moving gas on the bubble size is thus compensated, at least partially, by the delayed effect of the slowly moving gas. When the partial pressure difference of both gases has become zero the original condition as before changing the respiratory gas mixture is re-established. The change of the bubble size by alteration of the breathing gas mixture affects the partial pressure of the infused gas in the bubbles. The diluting effect of a fast-moving gas entering the bubbles on the outward-moving infusion gas enhances the growth of the bubbles by inhibition of this outward flux; the concentrating effect of a fast-moving gas leaving the bubbles on the outward-moving infusion gas enhances the decrease of the bubble size by facilitation of the outward flux. The influence of the total pressure difference between the intravascular bubbles (atmospheric plus pulmonary arterial pressure) and the alveolar space (atmospheric pressure plus small pressure changes due to the respiratory cycle) on the gas movement after altering the respiratory gas mixture will be minor since its magnitude is only small (10 to 30 mmHg) compared with that of the gas partial pressure gradients (500 to 600 mmHg). However, after disappearance of the partial pressure differences P_{ap} will again elicit a net gas movement from the bubbles so that the bubble removal will be equal to the continuing bubble supply, as was the case before changing the breathing gas mixture.

In view of this explanation of the processes influencing the bubble size the finding that a change of the breathing gas mixture from pure oxygen to 21% O_2 in helium causes a small increase of P_{ap} (Fig. 3) is somewhat surprising, since Krogh's diffusion coefficient of O_2 is higher than that of He. This seemingly paradoxical effect of He might be explained by a reversal of the preceding vaso-

dilative action of pure oxygen. The effect of changing the breathing gas from 21% O_2 in helium to pure oxygen on P_{ap} may be explained in the same way.

Turning from infusion to injection the effects of various breathing gases on circulatory and respiratory changes after venous gas injection (Results C) need further explanation. Venous gas injection causes a fast massive obstruction in the pulmonary circulation as evidenced by a rapid increase in P_{ap} . When the solubility of the injected gas is not too high, e.g., with CO_2 , the degree of obstruction will be similar for any gas (see chapter I). After the bubbles have reached the pulmonary arterioles, gas will move, due to different gas partial pressures, from the alveolar space into the intravascular bubbles or vice versa. Since helium and oxygen diffuse from the alveolar space into the bubbles faster than nitrogen, breathing a mixture of 21% O_2 and 79% He or pure oxygen induces enlargement of the bubbles and so a higher P_{ap} than during air breathing. Since within 2 min after the gas injection the diffusion processes have reached equilibrium the higher P_{ap} provides a faster removal of the bubbles so that the P_{ap} curve at 21% O_2 in helium or at 100% O_2 gradually returns to the P_{ap} curve during air breathing.

The changes of F_{ACO_2} are caused by changes in the distribution of ventilation and perfusion at constant artificial ventilation (see chapter IV). Increase in P_{ap} is accompanied by a decrease of F_{ACO_2} and vice versa. Contrary to the usual picture, Fig. 3 shows that when changing from 21% O_2 in helium to 100% O_2 breathing a decrease in P_{ap} is accompanied by a decrease of F_{ACO_2} ! This may be ascribed to a condition where the effect of a more equal distribution of the ventilation-perfusion ratio due to a decreased degree of embolization is exceeded by the unfavorable effect of oxygen on the regulation of the $\dot{V}_A/\dot{Q}$, i.e., by the fact that oxygen releases the hypoxic vasoconstriction in lung units with low ventilation-perfusion ratios, and thus further enhances their perfusion and de-

creases their ventilation-perfusion ratio (see chapter IV). These effects might be important in the treatment of pulmonary gas embolism, e.g., in decompression sickness.

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CHAPTER VI

INFLUENCE OF BODY POSITION ON THE EFFECTS OF PULMONARY GAS EMBOLISM

Summary

Previous investigations had shown that venous gas infusion in supine dogs at low rates (1 to 5 ml min^{-1}) induced circulatory and respiratory changes which reached a constant level about 15 min after starting the infusion. The most marked effects were an increase of pulmonary arterial pressure (P_{ap}) and a decrease of alveolar CO_2 fractional concentration (F_{ACO_2}). In the present study the influence of body position on the effects of venous gas infusion was examined. The body position of anesthetized dogs ventilated artificially varied between supine, right-side-down and left-side-down position. Without venous gas infusion the change of body position hardly affected circulatory and respiratory variables. However, during venous gas infusion a change of body position immediately elicited a rapid increase in P_{ap} and a decrease in F_{ACO_2} completed within a few seconds. Thereafter both variables gradually returned to their initial levels as before the change of body position. The extent of change in P_{ap} and F_{ACO_2} due to alteration of body position depended on the initial embolic level (determined by the rate of infusion and the nature of the gas used) and on the change of body position. The following hypothesis might explain these findings. In left-side-down position, e.g. the blood flow is mainly distributed to the lower lung whereas the bubbles preferentially follow the vessels to the upper lung due to their lightness. When the body position is altered to right-side-down, e.g., the normal redistribution of the blood flow to the lower lung is partially blocked now by the obstructing bubbles. To maintain the same blood flow an increased P_{ap} is needed to compensate for this increased resistance in the pulmonary circulation. The increased P_{ap} then provides an accelerated excretion of the intravascular bubbles so that the pulmonary vascular resistance diminishes again. At the moment the bubble excretion equals the bubble supply by the continuing infusion the original steady state is re-established.

Key words: pulmonary embolism - gas embolism - posture dog.

INTRODUCTION

Pulmonary gas embolism elicits changes in circulation and respiration. A distinction has to be made between the effects of gas injection (20 to 60 ml gas venously introduced within a few seconds) and of gas infusion (1 to 5 ml min⁻¹ gas continually infused into a vein during more than 15 min). After gas injection the most marked effects are a rapid increase in pulmonary arterial pressure (P_{ap}) and a synchronous decrease in alveolar CO₂ fractional concentration (F_{ACO_2}) at constant artificial ventilation. Within 30 to 60 s both variables reach their maximum and then return to their initial values within 10 to 20 min. During gas infusion P_{ap} and F_{ACO_2} change more slowly and reach a maximum after 10 to 15 min. This maximum is maintained as long as the infusion continues. After stopping the infusion both variables also return to their initial levels within 10 to 20 min. These results were obtained from anesthetized dogs in supine position (see chapter I and II). However, Fukuma et al. (1970) found considerable deviations in blood gas pressures depending on body position in the unanesthetized dog.

Several authors have demonstrated an influence of body position on the effects of venous gas injection (Cook et al., 1967; Durant et al., 1947; Durant et al., 1954; Holt et al., 1966). The most remarkable finding was the influence of the direction of the right ventricular outflow tract on the circulatory behavior after venous gas injection. When the right ventricle is filled with gas and blood, the gas bubble is situated in the upper part due to buoyancy. In left-side-down position where the right ventricular outflow tract is directed downwards, the ejection of blood is more effective than in supine or right-side-down position, where the right ventricular outflow tract is directed

upwards. In the latter situation bubbles pass the right half of the heart and cause massive obstruction in the pulmonary circulation. Thus the risk of circulatory failure after venous gas injection will be higher in supine or right-side-down position than in left-side-down position. However, during venous gas infusion when small gas bubbles arrive in the right ventricle after certain intervals, the effect on the circulation is quite different because no gas reservoir is formed in the right ventricle. The examination of these differences is the purpose of the present study.

METHODS

Five anesthetized mongrel dogs of either sex, weighing 15 to 25 kg were used. For a description of the preparation of the animals and of the procedure to measure circulatory and respiratory variables the reader is referred to chapter I and II.

In the present study the body position of the dog was varied between supine, right-side-down and left-side-down position. The body position during venous gas infusion was changed after the circulatory and respiratory variables had reached a constant level, as described in chapter I, II, III and IV.

RESULTS

The effects of venous gas infusion on diastolic pulmonary arterial pressure ($P_{ap\text{diast}}$) and alveolar CO_2 fractional concentration ($F_{A\text{CO}_2}$) were not influenced by body position. However, when the body position was changed during the gas infusion after $P_{ap\text{diast}}$ and $F_{A\text{CO}_2}$ had reached steady-state levels, this steady state was immediately disturbed. Figs. 1, 2, and 3 show that $P_{ap\text{diast}}$ increased to a maximum within a few seconds after any change of body position. Thereafter $P_{ap\text{diast}}$ re-

Fig. 1

Effect of change of body position from left-side-down to right-side-down and vice versa on diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration during venous infusion of O_2 at a rate of 2.4 and 3.2 ml min^{-1} and of air at a rate of 2.4 ml min^{-1} . Artificial ventilation was kept constant.

Fig. 2

Effect of change of body position from supine to right-side-down and vice versa on diastolic pulmonary arterial pressure and alveolar CO_2 fractional concentration during venous infusion of O_2 at a rate of 2.4 and 3.2 ml min^{-1} and of air at a rate of 2.4 ml min^{-1} . Artificial ventilation was kept constant.

Fig. 3

Effect of change of body position from supine to left-side-down and vice versa on diastolic pulmonary arterial pressure and alveolar CO₂ fractional concentration during venous infusion of O₂ at a rate of 2.4 and 3.2 ml min⁻¹ and of air at a rate of 2.4 ml min⁻¹. Artificial ventilation was kept constant.

turned to its initial level within about 5 min. At constant artificial ventilation $F_{A_{CO_2}}$ decreased almost synchronously with the increase in $P_{apdiast}$. After reaching the minimum value $F_{A_{CO_2}}$ also returned to its previous level.

The extent of change in $P_{apdiast}$ or $F_{A_{CO_2}}$ was largest after alteration from right-side-down or supine to left-side-down position and smallest after alteration from right- or left-side-down to supine position. Furthermore, it seemed that the extent of change in $P_{apdiast}$ and $F_{A_{CO_2}}$ also depended on the initial embolic level as seen from the steady state levels of $P_{apdiast}$ and $F_{A_{CO_2}}$ during 2.4 ml min^{-1} and 3.2 ml min^{-1} O_2 infusion and during 2.4 ml min^{-1} air infusion. Without gas infusion only minor changes were seen after alteration of body position.

DISCUSSION

Alteration of body position is accompanied by a change in hydrostatic pressure relations. Variations in body position in the horizontal plane, as applied in this study, hardly affect the systemic circulation because the arterial pressure far exceeds the changes in hydrostatic pressure. The low pressure system of the pulmonary circulation, however, is affected by such alterations in body position. These effects do not alter total blood flow, pulmonary arterial pressure or pulmonary vascular resistance but rather the blood flow distribution. The blood flow is mainly distributed to the dependent lung regions.

In the present study a marked difference was found in the behavior of the pulmonary circulation after alteration in body position during venous gas infusion in comparison with control condition. During venous gas infusion P_{ap} showed a rapid increase to a maximum some seconds after the change of body position, whereas in control condition P_{ap} remained practically constant. Knowledge of the fate of infused venous gas bubbles will throw some light on this problem. Gas bubbles intro-

duced venously are excreted from the pulmonary circulation into the alveolar space (see chapter III). Since the bubbles obstruct the pulmonary vessels before they are excreted, the pulmonary vascular resistance increases. This could be demonstrated by an increasing P_{ap} at constant cardiac output (see chapter I). The positive relationship between the increase in P_{ap} and the rate of bubble excretion suggested a causal connection. From this supposition a circulatory and respiratory steady state during continuing venous gas infusion, where the bubble supply equalled the bubble removal, could be explained. However, these findings still give no information about the distribution of the bubbles in the pulmonary circulation. According to buoyancy it may be expected that the bubbles preferentially float in the blood stream to the upper lung regions. This supposition can be demonstrated by a rapid change in the hydrostatic pressure relationship inside the pulmonary circulation due to turning the body.

As shown in Figs. 1, 2, and 3 there is a marked difference in the changes of P_{ap} and F_{ACO_2} at various alterations of body position. Two factors seem to be responsible for this finding: 1. the degree of rotation (90° or 180°) and 2. the difference in flow capacity of the right and left lung (about 1 : 2/3). When turning the body by 180° , e.g. from right- to left-side-down position, the blood flow should meet an increased vascular resistance in the pulmonary circulation because the dependent lung will now be blocked by gas bubbles at least partially. To maintain the same cardiac output a higher P_{ap} is necessary as could indeed be demonstrated in this study. The finding that the extent of a rise in P_{ap} depends on its initial level (as a measure of the degree of obstruction by the bubbles) is in agreement with this view. When turning the body by 90° , e.g. from supine to left-side-down position, a smaller part of the lower lung regions is obstructed resulting in a smaller increase in P_{ap} . The higher increase in P_{ap} after alteration from right- to left-side-down position compared with alteration from left- to right-side-down position can be explained by the

smaller flow capacity of the left lung so that the same quantity of bubbles produces a higher degree of obstruction in the left lung. The effects of turning the body from right- or left-side-down to supine position and vice versa have to be explained in this way too. The decrease of P_{ap} to its initial level after reaching the maximum might be due to bubble removal from the lower lung regions promoted by the increased P_{ap} . For most of the newly arriving bubbles supplied by the continuing infusion are distributed over the upper lung regions. Thus when the redistribution of blood flow and gas bubbles has been completed the initial steady state as before the change of body position is re-established. The changes in F_{ACO_2} running practically synchronously with those of P_{ap} can be explained by changes in the ventilation-perfusion ratio as described in chapter IV.

Only one study (Cook et al., 1967) could be found which investigated the distribution of gas bubbles and blood flow in the pulmonary circulation after venous gas administration. These authors injected 2 ml kg^{-1} air intravenously, followed immediately by a KCl-India ink bolus. This method is based on immediate cardiac arrest due to the KCl solution after reaching the coronary circulation so that the India ink distribution over the pulmonary circulation provides information about the blood flow just before the circulatory failure. Although the effects of gas injection differ from those of gas infusion these authors only found gas bubbles in the right lung (pink areas) in the left-side-down position, whereas the left lung showed a normal perfusion pattern (black areas). In supine or right-side-down position both lungs remained pink, showing that neither had been perfused. This latter finding is in agreement with that of Durant et al. (1954) and of Holt et al. (1966) and may be explained by ineffective contractions of the right ventricle since its outflow tract is filled with air.

In conclusion, the body position may be an important factor in the treatment of pulmonary gas embolism. In the dog studied here left-side-down position is preferable since the right ventricular contractions are

then more effective. This position has to be maintained to prevent an extra increase in pulmonary vascular resistance after alteration of the body position due to a redistribution of blood flow and gas bubbles.

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GENERAL CONCLUSIONS

- I. Pulmonary gas embolism induces circulatory and respiratory disturbances. The impact of these impairments depends on the following factors: 1) amount of penetrating gas, 2) speed of penetration, 3) physical properties of the gas, 4) body position, 5) respiratory gas mixture, and 6) performance of right ventricle.
- II. The most reliable indication of the severity of pulmonary gas embolism is the increase in pulmonary arterial pressure. When pulmonary ventilation is kept constant, also the decrease in alveolar CO₂ fractional concentration is a good measure of the extent of embolization. These two criteria are applicable only if cardiac output does not decrease appreciably. If this should occur the impairment of homeostasis is so serious that an irreversible shock is imminent.
- III. Venous gas bubbles are arrested in the pulmonary arterioles whereafter they are excreted into the alveolar space and leave the body with the expiration.
- IV. Hypoxemia during pulmonary gas embolism is primarily based on derangement of the distribution of the ventilation-perfusion ratio in the lungs. Application of hyperoxic gas mixtures relieves this hypoxemia but also enhances hypercapnemia. The latter may be combated by increase in pulmonary ventilation.
- V. Apart from the excretion of gas bubbles from the pulmonary circulation into the alveolar space there may also occur a gas transport from the alveolar space into the intravascular gas bubbles in certain conditions. This gas transport depends on the differences in gas partial pressures. Thus rapidly diffusing gases present in the alveolar space may temporarily augment the size of the intravascular gas bubbles.

- VI. Venous gas bubbles are distributed over the pulmonary circulation according to buoyancy. Any change in body position must induce an acute disturbance in the distribution of the gas bubbles and of the blood flow.

The chapters in this thesis will be offered to Pflügers Archiv for publication. The promotores J.A. Bernards and F. Kreuzer will then be mentioned as co-authors.

Effects of pulmonary gas embolism on circulation and respiration in the dog.

I. Effects on circulation.

II. Effects on respiration.

III. Excretion of venous gas bubbles by the lung.

IV. Origin of arterial hypoxemia during pulmonary gas embolism.

V. Gas movement between alveolar space and intravascular gas bubbles in the pulmonary circulation.

VI. Influence of body position on the effects of pulmonary gas embolism.

GENERAL SUMMARY

The purpose of this study was to investigate the pathophysiological processes accompanying pulmonary gas embolism and to use the findings if possible for advising in therapeutic measures. The gas bubbles were administered intravenously via infusion or injection in anesthetized dogs. The following gases were used: carbon dioxide, oxygen, air, nitrogen, helium and neon. The rates of infusion varied between 1 and 6 ml min⁻¹. Alternatively 10 to 60 ml gas was injected within 1 s. The most pronounced effect of venous gas administration was an increase of the pulmonary arterial pressure. Since cardiac output remained practically constant in most cases, the increase of pulmonary arterial pressure reflected an increase of resistance in the pulmonary circulation. Consequently the increase of pulmonary arterial pressure can be used to quantify the degree of embolization.

Mechanical obstruction by the gas bubbles is thought to be the major cause of the increased resistance in the pulmonary circulation because:

1. The degree of embolization increased with an increase of infusion rate as well as with the quantity of the gas injected (chapter I).
2. Embolization caused an increase in respiratory minute volume correlated to the degree of embolization (probably by way of reflex stimulation of "irritant receptors" by the emboli; chapter II).
3. At a constant amount of gas the degree of embolization was dependent upon the physical properties of the embolizing gas that determine the excretion rate into the alveolar space (chapters I and III).

The concept of gas emboli causing mechanical obstruction in the pulmonary vascular bed explains the following experimental results:

1. Change of composition of the breathing gas mixture during venous gas infusion appears to exercise a transient influence on the degree of embolization. The effect seen can be explained on basis of differences in diffusion rates between intravascular gas bubbles and alveolar space.
2. Change of body position during venous gas infusion led to an acute increase of the pulmonary arterial pressure. This effect can be explained by impairment of the distribution of gas bubbles over the upper and blood flow over the lower lung regions. When after changing the body position the dependent lung regions are partially blocked by gas bubbles a higher pulmonary arterial pressure is needed to overcome the higher hydrostatic pressure in the upper lung region. The gradual decrease of this pressure is again due to the excretion of the bubbles.

Our experiments do not support though not exclude the possibility of a vasoconstrictive component in the pulmonary circulation during pulmonary gas embolism. The changes in pulmonary gas exchange must mainly be attributed to a changed distribution of the ventilation-perfusion ratio in the lungs. Arterial hypoxemia is caused by an increase of the intrapulmonary shunt and arterial hypercapnemia by an increased dead space ventilation. Hyperventilation with a hyperoxic gas mixture can largely compensate for the consequences of the impaired ventilation-perfusion ratio in the lungs.

In pulmonary gas embolism the following therapeutic measures are suggested:

1. applying artificial hyperventilation with a slight hyperoxic gas mixture (25-30% O₂); see chapter II, IV and V,
2. positioning the body left-side-down; see chapter VI.

This, of course, must be accompanied by arresting the cause of the embolism and, when necessary because of imminent cardiac arrest by aspirating gas from the right half of the heart. Cardiac arrest should be treated by cardiac massage.

ALGEMENE SAMENVATTING

Het doel van deze studie was inzicht te verkrijgen in de pathofysiologische processen tijdens gasvormige longembolie en dit inzicht zo mogelijk toe te passen in adviezen voor het therapeutisch handelen. De gasbellen werden veneus toegediend via infusie of via injectie in genarcotiseerde honden. Als embolisatie gassen werden kooldioxyde, zuurstof, lucht, stikstof, helium en neon gebruikt. De infusiesnelheden varieerden tussen 1 en 6 ml min⁻¹ en de hoeveelheden gas, die binnen 1 seconde geïnjecteerd werden, tussen 10 en 60 ml. Het meest opvallende effect van veneuze gas-toediening was een toename van de druk in de longslagader. Aangezien de cardiac output in de meeste gevallen vrijwel constant bleef, vormde de druktoename in de longslagader een weerspiegeling van de toename van de weerstand in het longvaatbed. De druktoename in de longslagader kan dus gebruikt worden als graadmeter van de embolisatie. De volgende bevindingen wijzen op een mechanische obstructie van het longvaatbed door de veneus toegediende gasbellen:

1. De embolisatiegraad nam zowel toe bij een verhoging van de infusiesnelheid als bij een vergroting van de injectiehoeveelheid van een gas (hoofdstuk I).
2. Toename van de embolisatiegraad ging gepaard met een toename van het ademminuutvolume (dit wordt waarschijnlijk reflectoir veroorzaakt door prikkeling van "irritant receptors" door de embolieën; hoofdstuk II).
3. Tijdens toediening van eenzelfde hoeveelheid gas bleek de embolisatiegraad afhankelijk te zijn van de fysische eigenschappen van het embolisatiegas en daarmee van de uitscheidingsnelheid van het gas naar de alveolaire ruimte (hoofdstuk I en III).

Volgens bovengenoemde stelling kunnen ook de volgende bevindingen begrepen worden:

1. Verandering van samenstelling van het ademgasmengsel bleek tij-

dens veneuze gasinfusie een voorbijgaande invloed uit te oefenen op de embolisatiegraad. Ook na gasinjectie was een effect aantoonbaar van de samenstelling van het ademgasmengsel. Dit verschijnsel zou kunnen berusten op gasbewegingen tussen de alveolaire ruimte en de intravasculaire gasbellen op grond van verschillen in diffusiesnelheden.

2. Verandering van lichaamshouding tijdens veneuze gasinfusie veroorzaakte een acute toename van de druk in de longslagader. De gasbellen zijn voor de verandering van lichaamshouding voornamelijk terecht gekomen in de bovenliggende longdelen op grond van hun lichtheid ten opzichte van het bloed. Zij zullen dus na verandering van de lichaamshouding verstoppingen veroorzaken in lager gelegen longdelen. De bloedstroom wordt zo gedwongen hogere gebieden op te zoeken hetgeen alleen maar mogelijk is bij een toename van de druk in het arteriele deel van de longcirculatie. De geleidelijke daling van deze druk berust weer op de uitscheiding van gasbellen.

Bovenstaande resultaten maken een vaatvernauwende component in de longcirculatie tijdens gasvormige longembolie niet waarschijnlijk, doch deze kan niet volledig worden uitgesloten. De veranderingen, die optreden in de gasuitwisseling in de longen moeten hoofdzakelijk worden toegeschreven aan een veranderde distributie van de ventilatie-perfusie verhouding (hoofdstuk II en IV). De arteriele hypoxemie is te wijten aan een toename van de intrapulmonale shunt en de arteriële hypercapnemie aan de toegenomen dode ruimte ventilatie. Hyperventilatie met een hyperoxisch gasmengsel kan de optredende hypoxemie en hypercapnemie opheffen.

Het therapeutisch handelen bij gasvormige longembolie zou mede volgens de bevindingen van deze studie dienen te bestaan uit:

1. het stoppen van verdere binnendinging van gas in de circulatie,
2. het toepassen van kunstmatige hyperventilatie met een zwak hyperoxisch gasmengsel (25-30% O₂), zie hoofdstuk II, IV en V,
3. het aanbrengen en handhaven van de lichaamshouding in linker

- zijligging, zie hoofdstuk VI, en bij dreigende hartstilstand,
4. het aspireren van gas uit de rechter harthelft en eventueel het toepassen van hartmassage.

CURRICULUM VITAE

De schrijver is geboren in 1946 te Weert. In 1963 behaalde hij het HBS-B diploma aan de St. Paulus HBS te Tilburg. In 1967 werd de akte M.O. Lichamelijke Opvoeding behaald aan de Katholieke Academie voor Lichamelijke Opvoeding te 's Hertogenbosch. In de daarop volgende jaren werd het geven van onderwijs in de lichamelijke opvoeding gecombineerd met de studie in de geneeskunde aan de Katholieke Universiteit te Nijmegen. Na het behalen van het doctoraal examen in februari 1972 werd het vak fysiologie gedoceerd aan voornoemde K.A.L.O. (nu gesitueerd in Tilburg) en aan diverse opleidingen voor verpleegkundigen. Tegelijkertijd werd op part-time basis het hier besproken onderzoek verricht aan de afdeling fysiologie van de Faculteit der Geneeskunde. In de overblijvende tijd werden, overigens niet zonder moeite, de co-assistentenschappen gevolgd ter verkrijging van toelating tot het artsexamen. In november 1976 zou dit worden afgelegd. Met ingang van 1 juli 1975 is de schrijver benoemd tot wetenschappelijk medewerker aan de Rijksuniversiteit Limburg als lid van de capaciteitsgroep fysiologie. Zijn research activiteit is nu vooral gericht op de inspanningsfysiologie en wel speciaal de aspecten van bloedsomloop en ademhaling. Daarnaast zal de promovendus deelnemen aan het onderwijs aan de medische studenten.

STELLINGEN

1. De longcirkulatie vormt een effectieve barrière tegen veneuze gasembolieën.
2. Veneuze gasembolieën worden in de longen uitgescheiden.
3. De gestoorde gasuitwisseling in de longen, die optreedt bij longembolie, is hoofdzakelijk te wijten aan een ongunstige ventilatie-perfusie verhouding.
4. Wanneer slechts één long getroffen wordt door één of meerdere embolieën, dan heeft die lichaamshouding de voorkeur, waarbij de niet-aangedane long naar beneden gericht is.
5. Bij gasvormige longembolie is overschakeling van lucht op een hyperoxisch ademgasmengsel gevaarlijk vanwege een tijdelijke vergroting van de gasbellen in de longcirkulatie.
6. In het medisch onderwijs zou meer aandacht geschonken moeten worden aan de didaktische en methodische vorming van docenten.
7. Het objectief vaststellen van een waarderingscijfer voor een stage of examen door één persoon is niet goed mogelijk.
8. Bij de opleiding van artsen zou meer aandacht besteed moeten worden aan attitude-vorming. Hier zouden opleiders en assistenten mede van kunnen profiteren.
9. Het meten van fysieke kwaliteiten bij een topsporter dient zoveel mogelijk te gebeuren via imitatie van bewegingsvormen uit de wedstrijdsituatie.
10. In de opleiding van leraren lichamelijke opvoeding zou het pakket van praktische vakken aangepast moeten worden aan hun respectievelijke importantie in de huidige maatschappij.
11. Lichamelijke vorming moet in het studiepakket van het wetenschappelijk onderwijs opgenomen worden.
12. Kompensatiemogelijkheden van onvoldoende cijfers door cijfers van niet-verwante vakken bij examens vormt een ernstige aantasting van de waarde van het diploma.