Experimental Studies on the Oxygen Tension in the Myocardium and Changes of Cardiac Function in Hypoxia

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ABSTRACT. Using adult mongrel dogs, experiments were performed to elucidate the relationship between the changes in the myocardial oxygen tension (PmO_2) in anoxia and disturbances of cardiac function. Dogs, forced to inspire 100% N_2, sufferd from a respiratory arrest after 5 min, and developed acute anoxia. However, by 100% O_2 inhalation 2 min after the onset of the respiratory arrest, the anoxia rapidly resolved. The arterial oxygen tension (PaO_2), left intra ventricular oxygen tension ($PLvO_2$) and PmO_2 showed the most pronounced fall 2 min after the respiratory arrest induced by N_2 inhalation. The arterial carbon deoxide tension ($PaCO_2$) decreased until the respiratory arrest, after which it started to rise. When inhalation of 100% O_2 was initiated at the anoxia, the PaO_2, $PLvO_2$ and PmO_2 recovered within 1 min followed by a rise beyond the baseline value. Left ventricular end-diastolic pressure (LVEDP), left atrial mean pressure (LAm), left ventricular systolic pressure (LVSP), aortic mean pressure (Aom), maximum rate of force development by left ventricle (LVmax. dp/dt), total peripheral resistance (TPR), cardiac output (CO) and heart rate (HR) were measured. At the onset of anoxia, these parameters decreased sharply. When inhalation of 100% O_2 was initiated within 2 min of the respiratory arrest, these disturbances of cardiac function recovered rapidly. The fall of PmO_2 plays an important role in the impairment of cardiac function.—KEY WORDS: cardiac function, hypoxia, PmO_2.

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Tissue anoxia developed in the presence of arterial hypoxemia caused by a decrease in alveolar oxygen concentration, mixing of venous blood through a shunt, anemic hypoxia due to the decrease of blood hemoglobin (Hb) concentration or biochemical changes of Hb, stagnant or circulatory hypoxia, oxygen requirement which exceeded its supply, and metabolic or histotoxic anoxia [14]. Anoxia might be defined best as a deficient state of oxygen supply for normal function of cells and body tissues due to inadequate oxygen saturation of the blood.

When tissues of a living organism developed anoxia, carbonate developed excessively, resulting in a state of asphyxia. The progress of tissue damage was strongly influenced by the time factor as well as the differing sensitivity to anoxia of each tissue and organ in the body. The central nervous system was most sensitive to anoxia, while the skeletal muscle and peripheral nerves might tolerate anoxia for a relatively long time [13]. In anoxia, pulmonary and cardiac function and blood properties were strongly influenced by the amout of oxygen supplied to the tissue and oxygen tension [15].

After respiratory and cardiac arrest leading to anoxia, the central nervous system is damaged irreversibly. Brain death plays an important role in the clinical handling of small animals. In small animals, anoxia develops in response to various causes such as airway obstruction, ventilation failure, respiratory failure due to various anesthetic

procedures, and respiratory arrest because of shocks. The exact process which takes place between respiratory arrest and cardiac arrest presents a problem, and the relationship between the oxygen uptake by the organism and cardiac function is quite important. If a clear causal relationship for the oxygen uptake and cardiac function can be elucidated, clinically adequate measures may be developed to manage anoxia.

MATERIALS AND METHODS

Nine adult mongrel dogs (5 males and 4 females) with a range of body weight from 9.0 to 19.9 kg (11.7 kg on average) were used. Healthy animals were selected based on a general clinical examination, hematology, electro- and phono-cardiogram and chest X-ray.

As shown in Fig. 1, the dogs underwent thoracotomy under halothane anesthesia (OF), the heart was exposed under direct vision, and various instruments were attached to measure the myocardial oxygen tension (PmO_2) and cardiac function, followed by chest closure. The anesthetic depth was maintained at Stage 3, Phase 2, within a range of acceptable variation. Body fluid status was maintained by a intravenous lactated Ringer solution infusion at a rate of 10 ml/kg/hr after anesthetic induction.

After all instruments had been attached and the detectors had been stabilized, control values were obtained. The animals were then allowed to breathe 100% N_2 until respiratory arrest occurred. Artificial respiration with 100% O_2 was instituted to reverse anoxia. Throughout this period, PmO_2, arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), and cardiac function were measured in chronological sequence. The oxygen tension (PO_2) and cardiac function were measured using the following methods.

Oxygen tension: PmO_2 and left intra

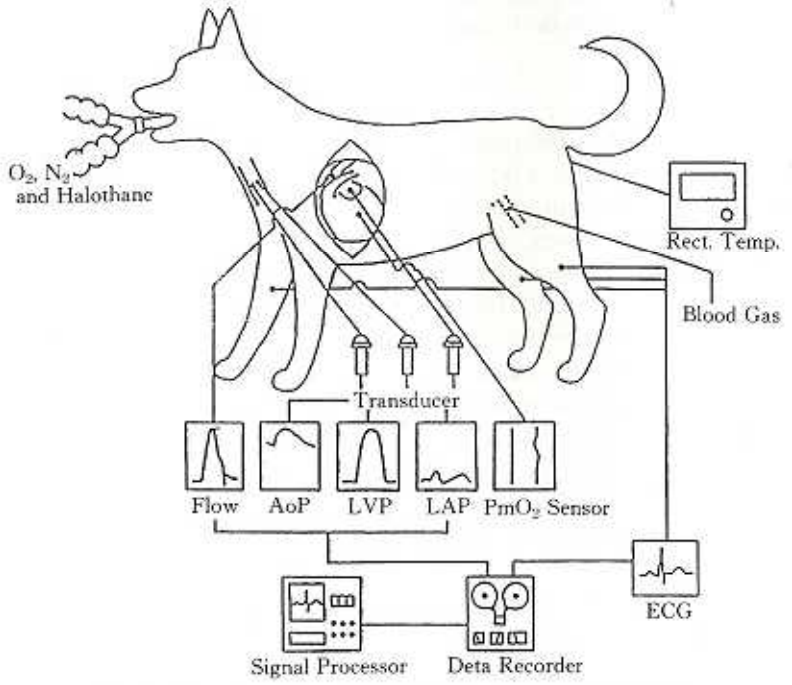

Fig. 1. Experimental method of PmO_2 and cardiac function.

ventricular oxygen tension ($P_{LV}O_2$) were measured using a PO_2 sensor (M-HOS™) and an analytical system (PO-2080™: Mitsubishi Rayon Co., Ltd.). The responsiveness of the PO_2 sensor was confirmed with an I.L. meter (Model Micro 13) beforehand. The PaO_2 and $PaCO_2$ in the abdominal aorta were measured by the I.L. meter from blood obtained from the right femoral artery using a catheter.

Arterial blood pressure and intracardiac pressure: The aortic systolic and diastolic pressures (Aos and Aod) were measured in the right carotid artery with a catheter. The aortic mean pressure (Aom) was calculated by the formula:

$$\text{Aom} = \frac{\text{Aos} + \text{Aod}}{2}$$

The left ventricular systolic and end-diastolic pressures (LVSP and LVEDP) were measured by a catheter inserted into the left carotid artery. The maximum rate of force development by left ventricle (LV max.dp/dt) was measured by these pressure curves. The left arterial mean pressures (LAm) was measured by a catheter directly inserted into the left atrium.

Among these values, LVEDP and LAm were used as preload indices, and Aom and LVSP afterload ones. LV max.dp/dt served as an index of cardiac contractility.

Cardiac output: A probe was attached to the ascending aorta. Stroke volume (SV) was measured by an electromagnetic flowmeter. The cardiac output (CO) obtained from the SV and heart rate (HR) was divided by the body weight in order to remove the variation of body weight as the following formula:

$$CO^{1)}(\text{ml/kg/min}) = SV \times HR/BW$$

Total peripheral vascular resistance (TPR): The TPR was calculated from Aom and CO using the following formula:

$$TPR\ (\text{dyne·sec/cm}^5) = (Aom/CO^{2)}) \times 80^*$$

*1mmHg/l/min=1333dyne/cm^2/1000cm^3/60sec=80dyne·sec/cm^5

where $CO^{2)}$(ml/min)=SV×HR

Heart rate: The HR was calculated by the ECG by the standard limb lead II.

Statistical analysis: The levels of statistical significance were $p<0.05$ and 0.01, and all data were presented as mean ±SD. Paired data were compared using Student's *t*-test.

RESULTS

Changes in PmO_2: The PmO_2 was measured by the PO_2 sensor inserted into the intermediary zone of the left ventricular myocardium and averaged 49.1±11.1 mmHg (n=7) in the controls. After 100% N_2 inhalation, a respiratory arrest occurred 5 min later, with a transition from hypoxia to anoxia. The mean PmO_2 at the respiratory arrest averaged 16.1±8.8 mmHg. After 2 min respiratory arrest, the mean PmO_2 decreased further to 9.3±8.8 mmHg (n=6), a significant fall compared with the control value ($p<0.01$). Artificial respiration with 100% O_2 after 2 min respiratory arrest led the PmO_2 to rise rapidly and the anoxia resolved with a reappearance of spontaneous respiration. The PmO_2, measured 2 min after inhalation of 100% O_2, averaged 50.7±29.1 mmHg (n=7), a significant increase compared with two minute later from respiratory arrest ($p<0.01$). The PmO_2 remained between 32.2±14.9 and 49.7±33.7 mmHg for 10 min after the initiation of O_2 inhalation (Fig. 2).

Changes in $P_{LV}O_2$ and PaO_2: The control $P_{LV}O_2$ values averaged 110.4±50.2 mmHg (n=7), and the control PaO_2 values 115.7±11.7 mmHg (n=9). Both sets of values were found in the same range.

The $P_{LV}O_2$ and PaO_2 at the time of anoxia

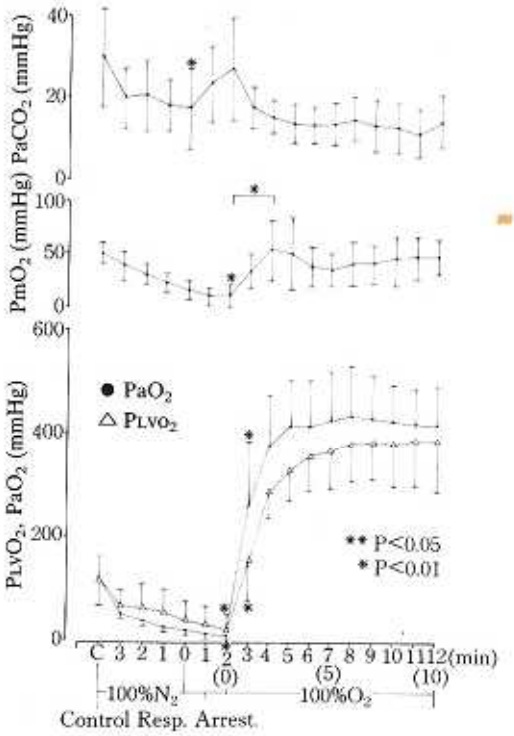

Fig. 2. Changes of blood and cardiac muscular tissue gases during the acute anoxia and resuscitation.

and respiratory arrest after 5 min of 100% N_2 inhalation averaged 39.3±37.5 mmHg, and 21.5±7.9 mmHg (n=7), respectively. After 2 min of respiratory arrest, the $P_{LV}O_2$ averaged 21.3±31.4 mmHg (n=6) and PaO_2 11.3±4.5 mmHg (n=7). Both values respresented a significant fall from the control value ($p<0.01$).

When artificial respiration with 100% O_2 was initiated 2 min after respiratory arrest, a rapid recovery was noted within 1 min with the mean $P_{LV}O_2$ of 166.3±88.1 mmHg (n=6) and the mean PaO_2 of 268.4±121.7 mmHg (n=8). Both represented a significant rise over the control value ($p<0.01$). The $P_{LV}O_2$ averaged 383.3±72.8 mmHg (n=7) after 8 min, and 391.0±87.1 mmHg after 10 min. The mean PaO_2 was 420.0±89.2 mmHg (n=8) after 3 min of 100% O_2 inhalation and rose to the mean of 438.7±103.0 mmHg after 10 min (Fig. 2).

Changes in $PaCO_2$: Blood samples were obtained from the abdominal aorta and $PaCO_2$ was measured using the I.L. meter. The $PaCO_2$ value at the onset of anoxia after 100% N_2 inhalation averaged 17.7±9.5 mmHg (n=8), a significant decrease from the control value ($p<0.01$). After 2 min from respiratory arrest, the mean value was 27.0±12.6 mmHg (n=7), approaching the control value. From 1 to 10 min after the initiation of 100% O_2 inhalation, the mean value of 17.5±5.0 mmHg (n=8) was maintained (Fig. 2).

Changes in Aom: Aortic pressure was measured by a catheter inserted to the origin of the aorta. Aos and Aod were measured based on the aortic pressure wave pattern and were used for calculation of Aom. The control Aom value averaged 99.9±6.8mmHg (n=9). A small increase was seen until 1 min prior to the respiratory arrest induced by 100% N_2 inhaltion. After the respiratory arrest, the values decreased, reaching the mean of 81.0±6.2 mmHg after 2 min, a significant decrease from the control value ($p<0.05$). Within 1 min after resuscitation with 100% O_2 inhalation, a rapid increase to the mean of 158.0±21.8 mmHg (n=5) was observed, a significant increase over the control value ($p<0.05$). A slight decrease was noted until 10 min after the beginning of O_2 inhalation, but the value remained higher than the control within the range of 163.9±18.0 to 129.2±11.7 mmHg (Fig. 3).

Changes in LVSP: Left ventricular pressure was measured by a catheter inserted into the left ventricular cavity. Based on the ventricular pressure wave pattern, LVSP and LVEDP were measured. The control LVSP value averaged 128.4±8.1 mmHg (n=8). In response to 100% N_2 inhalation, a gradual rise was noted up to 1 min prior to the respiratory arrest. At 2 min after the respiratory arrest, the mean value of

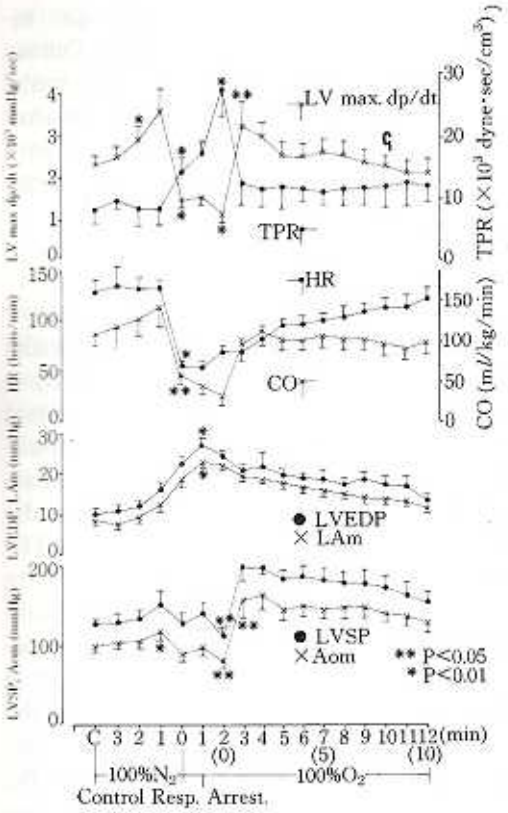

Fig. 3. Hemodynamic changes occurring during acute anoxia and resuscitation.

115.4±10.0 mmHg (n=8) was obtained, a significant fall from the control value ($p<0.05$). After inhalation of 100% O_2, a rapid recovery occurred within 1 min, reaching mean levels of 214.4±24.1 to 157.0±14.9 mmHg.

Changes in LVEDP: Control LVEDP values averaged 10.5±1.1 mmhg (n=8). A gradual rise was noted during 100% N_2 inhalation, reaching the mean of 27.0±1.7 mmHg (n=8) after 1 min of respiratory arrest, a significant rise above the control value ($p<0.01$). After inhalation of 100% O_2, a gradual fall was noted. Up to the 10 min point, however, the values remained within the range of 24.6±1.1 to 13.9±1.8 mmHg (Fig. 3).

Changes in LV max.dp/dt: The LVmax.dp/dt was calculated using the left ventricular pressure wave, and control values averaged 2,296±247 mmHg/sec (n=8). During 100% N_2 inhalation, the value increased to 2,888±339 mmHg/sec 2 min prior to the respiratory arrest, a significant rise from the control value ($p<0.01$). A further increase was noted immediately prior to the respiratory arrest. At the onset of anoxia, during the respiratory arrest, a sudden fall occurred, showing the value of 1,112±149 mmHg/sec (n=8), a significant fall from the control value ($p<0.01$). After 1 min of 100% O_2 inhalation, the mean value increased to 3,274±588 mmHg/sec, a significant rise over the control value ($p<0.05$). It dropped off gradually until approaching the control value after 10 min (Fig. 3).

Changes in LAm: The LAm was calculated from the left atrial pressure wave pattern by a catheter inserted into the left atrium. The control LAm value averaged 8.3±1.0 mmHg (n=8). After inhalation of 100% N_2, respirations stopped and anoxia ensured with the LAm mean value of 23.2±1.5 mmHg (n=8), a significant increase over the control value ($p<0.01$). After inhalation of 100% O_2, a gradual decrease was seen until the value of 11.1±1.2 mmHg was obtained after 10 min (Fig. 3).

Changes in HR: The cardiac rate was calculated from the lead II ECG and averaged 127.8±11.3 beats/min (n=9) in the controls. After inhalation of 100% N_2, respiration ceased and anoxia developed. A rapid fall in HR occurred at the same time, reaching the average of 54.3±4.2 beats/min, a significant decrease from the control value ($p<0.01$). Immediately after the inhalation of 100% O_2, the HR started to recover slowly, reaching 122.7±10 beats/min on average after 10 min (Fig. 3).

Changes in CO: According to the method previously described, the mean CO, measured at the ascending aorta, was

109.0±14.0 ml/kg/min (n=6). A gradual increase was noted after inhalation of 100% N_2, and reached the mean of 140.9±24.7 ml/kg/min (n=6) 1 min prior to the respiratory arrest. A sudden decrease followed the respiratory arrest and anoxia, reaching the mean of 57.0±8.1 ml/kg/min (n=6), a significant fall from the control value ($p<0.05$). The decrease continued for 2 min during the respiratory arrest, but began to recover as soon as the 100% O_2 inhalation was started. Two min after the initiation of O_2 inhalation, the mean value was 111.3±4.4 ml/kg/min (n=4). Up to the 10 min point, the values remained within the range from 105.1±11.3 to 91.9±13.0 ml/kg/min (Fig. 3).

Changes in TPR: The TPR was obtained by the method previously described based on the values of Aom and CO. Control values averaged 7,933±2,166 dyne·sec/cm^5 (n=6). After inhalation of 100% N_2, a rise in TPR occurred, reaching the mean value of 27,697±4,658 dyne·sec/cm^5 (n=5) 2 min after the respiratory arrest, a significantly higher value than in the control ($p<0.01$). At the moment of 100% O_2 inhalation, a sudden decrease occurred in each case, and the average in three cases was 12,468±3,086 dyne·sec/cm^5. The values fluctuated within a range from 12,772±4,042 to 11,249±3,861 dyne·sec/cm^5 for the next 10 min of O_2 inhalation (Fig. 3).

Changes in ECG: The wave patterns, amplitudes and intervals of the P wave, QRS complex and T wave were normal in the ECG from standard limb lead II. The PQ and QT intervals were also within the normal range. The ECG at the onset of anoxia and respiratory arrest revealed a bradycadia with prolonged R-R intervals. There was a dissociation of potential conduction between the atrium and ventricle which resulted in an abnormal picture of atrioventricular dissociation. After 2 min of respiratory arrest, the QRS complex appeared abnormal, indicating an intraventricular conduction defect. During resuscitation with 100% O_2, the initial ventricular tachycardia was noted, but after 2 min, sinus rhythm was achieved, and a completely normal ECG was obtained after 10 min.

DISCUSSION

Anoxia and respiratory arrest in actual clinical situations were complicated by a significant acidosis [2, 6] and the survival rate decreased sharply 2 min after respiratory arrest [4–7]. Therefore, the point 2 min after respiratory arrest was regarded as the limit for resuscitation by O_2 alone [17]. The oxygen tension in anoxia fell most rapidly in the kidney, followed by the liver, subcutaneous tissue and cerebrum. The decrease of oxygen tension stopped fastest in the brain, followed by the liver, kidney and subcutaneous tissue. When effective resuscitation was instituted within 2 min from the onset, the disturbance in each organ recovered completely. After 8 min, however, a serious disturbance remained even if the life was saved [10]. Treatments for hypoxia might include pressor therapy [12, 16], treatment with THAM [9, 11] and hyperbaric oxygen therapy [3].

In respiratory arrest, both the occurrence of hypoxia in each organ and tissue and the time elapsed after the onset are important factors for treatment. The occurrence of hypoxia depends on changes of oxygen tension in each organ and tissue.

In this experiment, acute anoxia caused by a respiratory arrest was artificially produced with a transition from hypoxia to anoxia. About 2 min after the onset of respiratory arrest, resuscitation using the inhalation of 100% O_2 was realized within 1 min. Cardiac function during this period showed a marked decrease along with a fall in PmO_2. A recovery, however, occurred

within 1 min of resuscitation by 100% O_2 inhalation. After more than 3 min of respiratory arrest, however, the recovery of cardiac function was slow and the survival rate and the rate of successful resuscitation were significantly diminished [17].

These data indicated a sudden decrease in oxygen in the living organism during the transient from hypoxia to anoxia of the myocardium. Especially, since the fall of PmO_2 caused a marked disturbance of myocardial activity, it might play an important role in the development of cardiac function disturbance. The cardiac function was recovered prior to the peak in PmO_2, therefore, a small change of PmO_2 might have marked influence on the cardiac function. The progression of irreversible change in the central nervous system from 3 to 8 min after respiratory arrest was extremely important in clinical therapy [8]. In our data, O_2 inhalation instituted within 2 min of respiratory arrest made resuscitation successful. However, only 1 min delay, might result in high occurreuce of irreversible change in the organism [17]. The time for application of emergency measures is rather limited. During the marked decrease in myocardial oxygen supply, the myocardium can utilize anaerobic metabolism, being mediated by glycolysis, in order to maintain a normal rhythm. However, the efficiency of energy production decreased, and myocardial contraction and action potential generation were impaired [1, 18]. Cardiac dysfunction was influenced by myocardial energy metabolism, and the decrease of PmO_2 in anoxia was directly related to both myocardial energy metabolism and the development of cardiac dysfunction. For the treatment for cardiac dysfunction due to anoxia, an emergency oxygen supply should be administered within 2 min after the onset of respiratory arrest in order to facilitate the restoration of PmO_2.

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要　　約

無酸素症の心筋組織内酸素分圧と心機能の変化に関する実験的研究：中村　志・吉野千太郎・飯田英治・若尾義人・武藤　眞・高橋　貢（麻布大学獣医学部獣医外科学教室）――健康な雑種犬を使用して，無酸素症におけるP_mO_2の変動と心臓機能障害との関係を解明するための実験を行った．健康犬に100% N_2を吸入させると約5分を経過して呼吸が停止し，急激な無酸素症が発現した．呼吸停止後無酸素症に陥り，2分を経過した時点で100% O_2を吸入させると，無酸素症は急激に回復した．100% N_2吸入で呼吸が停止し無酸素症が実現してから，2分を経過した時点でP_aO_2，$P_{LV}O_2$ならびにP_mO_2が最も低下した．この場合，P_aCO_2は，呼吸停止時までは低下したが，呼吸停止と同時に上昇した．無酸素症に陥った時点で，100%O_2の吸入を行った結果，P_aO_2，$P_{LV}O_2$ならびにP_mO_2は約1分以内に回復し，その後は正常値を上回って上昇した．心機能のパラメータとしてLVEDP, LAm, LVSP, Aom, LV max. dp/dt, TPR, CO ならびに HR を計測した結果，無酸素症に陥った時点でこれらのパラメータは著しく低下し，心室内伝導障害もみられた．しかし，呼吸停止後2分以内に100% O_2の吸入を行うと，これらの心機能障害は速やかに回復することが確認された．このことからP_mO_2の低下が心機能障害を発現する大きな要因となることが明らかとなった．