The Beneficial Effects of 40% and 100% O₂ Inhalations on Acutely-Induced Myocardial Ischemia in Dogs

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ISHIKAWA, K., KANAMASA, K., YAMAKADO, T. and KATORI, R. *The Beneficial Effects of 40% and 100% O₂ Inhalations on Acutely-Induced Myocardial Ischemia in Dogs.* Tohoku J. exp. Med., 1986, **149** (2), 107-117 — The effectiveness of O₂ inhalation on the acutely-induced ischemic myocardium in dogs was investigated. In 22 open-chest mongrel dogs, the left anterior descending coronary artery was partially occluded to reduce coronary flow. The regional coronary vein accompanying the artery was cannulated to obtain coronary venous blood. Switching of inspiratory gas from room air to 40% O₂ produced an elevation of coronary venous O₂ saturation from 35.8 ± 12.7 (s.d.) to $41.1 \pm 11.9\%$ and shifting of myocardial lactate production to utilization (from -0.9 ± 36.9 to $5.0 \pm 36.7\%$), indicating that 40% O₂ inhalation ameliorated ischemia. Application of 100% O₂ inhalation caused even more beneficial effects; coronary venous O₂ saturation was elevated to $50.6 \pm 12.6\%$ and myocardial lactate extraction was improved to $7.8 \pm 40.5\%$. The present study indicated that 40% O₂ inhalation was effective and 100% O₂ inhalation even more effective in ameliorating acutely-induced myocardial ischemia. Decreases in myocardial contractile force and left ventricular size and suppression of sympathoadrenal activity might be possible mechanisms for these beneficial effects. ——— O₂ inhalation therapy; myocardial infarction; angina pectoris; coronary circulation

Of the various regimens proposed for the treatment of myocardial infarction, the effectiveness of only a few has been confirmed. Intravenous (i.v.) injection of lidocain, essential for treatment of arrhythmias in acute myocardial infarction (Harrison and Berte 1982), is not used in every patient. Not all clinics perform routine application of warfarin in all cases, to include uncomplicated myocardial infarction, even though a number of reports show positive results in the secondary prevention of myocardial infarction (Loeliger 1981). A report from the International Society and Federation of Cardiology (ISFC) concluded that no clear recommendations are possible on the use of platelet-active drugs for patients with myocardial infarction (Schettler et al. 1982). Recently, i.v. thrombolysis (Maddahi et al. 1983) has been advocated for treatment of acute myocardial infarction but

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others consider the clinical value of intracoronary thrombolysis to still be experimental (Furberg 1984). In this flood of new treatments the older ones are dropping behind with questions regarding their efficacy being left unanswered. It is surprising that even the usefulness of O₂ inhalation therapy, one of the oldest and most widely applied treatments, is also still an unsettled question. This paper confirms the efficacy of 100% O₂ inhalation in treatment of acutely-induced myocardial ischemia and discusses the conflicting information (Saltzman 1975; Ishikawa et al. 1983) currently available on this conventional treatment.

MATERIALS AND METHODS

In 22 mongrel dogs weighing 20 ± 9 (mean $\pm$ s.d.) kg, anesthesia was performed with phenobarbital, 20–30 mg/kg i.v., and the chests were opened at the left 4–5th intercostal space under positive pressure breathing. Respiration rate, tidal volume and end-expiratory pressure were adjusted so as to maintain an arterial Po₂ of 75–80 mmHg and a Pco₂ of 35–40 mmHg during room air breathing. The heart was exposed on the pericardial cradle. The left anterior descending coronary artery (LAD) was dissected approximately 1 cm downstream of the bifurcation of the left circumflex artery (LCX) and an electromagnetic flowmeter probe (MF-46, Nihon Kohden, Tokyo) was installed. Approximately 5 mm downstream to this probe, a silk suture constrictor was attached to make a partial occlusion of the coronary artery. This constrictor (Ishikawa et al. 1974a) has been proven to be a suitable method for making a partial constriction of the artery because it is easily attached to the vascular wall and is very light so as to move freely with the movement of the heart. The regional coronary vein accompanying the artery was cannulated for regional coronary venous sampling (Fig. 1). A Walton-Brodie strain gauge arch (HD-1T, Nihon Kohden) was sutured on the left ventricular free wall parallel to the superficial layer of the myocardium

Fig. 1. Schematic representation of the protocol and experimental design.

to extend approximately 20% of its initial length. This was used to measure any existing force in the epicardial layers of the heart (Cotten and Bay 1956). A cotton swab, 2 mm in diameter and dipped in physiological saline was placed on the epicardium to record an epicardial electrocardiogram (ECG). Aortic flow was measured using an electromagnetic flowmeter (FM-46, Nihon Kohden) installed at the aortic root. The tip of a catheter was advanced to the ascending aorta to measure aortic pressure as well as to obtain arterial blood samples. All recordings were made on an 8-channel inkwriting oscillograph (RM-85, Nihon Kohden). Sixteen consecutive tracings of myocardial force and epicardial ECG were synchronized with the R wave of the ECG to build an oscilloscope trace (addscope ATAC-260, Nihon Kohden). Blood samples from the artery or coronary vein were analyzed for blood O₂ content (LEX O2 CON, Lexington Instruments, Waltham, USA), for hemoglobin, Po₂, Pco₂, pH and O₂ saturation (ABL 1 Radiometer, Denmark) and for lactate concentration.

The experimental protocol is shown at the top of Fig. 1. All measurements were performed to serve as control (A) before making the partial occlusion of the coronary artery. Then, the LAD was constricted so that the phasic flow through the artery was diminished and myocardial contractile force was reduced. All measurements performed at control were repeated one hr after partial occlusion (B). The inspiratory gas was then switched from room air to 40% O₂/60% N₂ at one atmosphere. This was maintained for 15 min, all measurements being repeated again during the last 5 min (C). The inspiratory gas was next switched to 100% O₂ at one atmosphere and measurements again performed (D). In order to exclude time course changes during the partial occlusion and also to confirm the re-

Fig. 2. Changes in arterial Po₂, heart rate, aortic pressure, aortic flow and myocardial contractile force. * $p < 0.05$; ** $p < 0.01$ against each preceding value.

TABLE 1. *Effects of 40% and 100% O₂*

	Control (A)	Air (B)
Heart rate(beats/min)	169 ± 29(± s.d.)	170 ± 19
Mean aortic pressure(mmHg)	109 ± 32	92 ± 28**
Aortic flow(ml/min)	629 ± 462	496 ± 370
Myocardial contractile force(%)	100	66 ± 20**
Epicardial ECG ST elevation(mV)	3.4 ± 2.2	4.4 ± 2.2*
Arterial Po ₂ (mmHg)	78.6 ± 7.1	80.7 ± 7.4
Pco ₂ (mmHg)	38.1 ± 6.8	
pH	7.370 ± 0.077	
O ₂ content(ml/100 ml)	18.8 ± 1.9	18.8 ± 1.8
Coronary venous Po ₂ (mmHg)	29.3 ± 3.8	23.5 ± 3.9*
O ₂ saturation(%)	52.0 ± 6.8	35.8 ± 12.7**
Pco ₂ (mmHg)	48.2 ± 10.3	53.6 ± 9.0*
pH	7.348 ± 0.058	7.313 ± 0.076**
O ₂ content(ml/100 ml)	9.0 ± 3.7	6.4 ± 3.6*
Coronary AV O ₂ difference(ml/100 ml)	9.4 ± 2.8	12.0 ± 2.9*
Myocardial O ₂ extraction(%)	48.1 ± 14.5	63.6 ± 15.3*
Myocardial lactate extraction(%)	28.0 ± 16.4	−0.9 ± 36.9*

* $p < 0.05$; ** $p < 0.01$. against values in the preceding condition.

producibility of the experiment, the 100% O₂ (D) was switched back to 40% O₂/60% N₂ (E) and then back to room air (F), all measurements being repeated each time. Approximately 75 min were required to complete one cycle (from B to F). If, while going from B to F, the heart rate or the mean aortic pressure changed more than 10 beats/min or 10 mmHg, respectively, the experiment was discarded because such hemodynamic shifts could have modified our results. Changes in parameters were expressed in terms of mean ± s.d. Differences in mean values were analyzed using Student's *t*-test for paired samples or with non-paired *t*-test and considered to be significant when *p* values were less than 0.05.

RESULTS

All values measured between control (A) and the final phase (F) are shown in Table 1. Almost no change in heart rate was seen throughout the entire course of the experiment (Fig. 2). A drop in aortic pressure and also a drop in aortic flow were evident after partial occlusion of the coronary artery. These were accompanied by a marked reduction in myocardial contractile force. Coronary blood flow at control (A) was 21 ± 7 ml/min (mean ± s.d.). This was reduced by less than 5 ml/min in most of the experiments which was beyond the accuracy of the conventional flow measurements and those values were not listed. Myocardial contractile force, which was reduced to 60% of control after partial occlusion,

inhalation on the ischemic myocardium

Coronary artery constricted			
40%O ₂ (C)	100%O ₂ (D)	40%O ₂ (E)	Air (F)
169 ± 20	166 ± 23	165 ± 21	169 ± 18
88 ± 29*	88 ± 27	87 ± 27	86 ± 28
492 ± 378	523 ± 390*	523 ± 385	528 ± 387
65 ± 19	61 ± 18*	62 ± 19	68 ± 23
3.4 ± 1.9**	3.2 ± 1.2	3.8 ± 1.7*	3.9 ± 1.9
141.4 ± 16.0**	412.4 ± 67.3**	143.7 ± 27.3**	83.2 ± 5.6**
39.4 ± 7.3	39.0 ± 8.1		
7.356 ± 0.082	7.362 ± 0.087		
19.7 ± 1.9**	20.8 ± 1.9**	19.6 ± 1.7**	18.7 ± 1.7**
25.7 ± 4.1**	30.2 ± 4.9**	26.5 ± 4.0**	24.2 ± 4.2**
41.1 ± 11.9**	50.6 ± 12.6**	43.5 ± 11.0**	37.5 ± 12.0**
54.6 ± 9.6	55.8 ± 9.5	54.0 ± 9.4*	52.8 ± 9.4
7.312 ± 0.081	7.301 ± 0.073*	7.316 ± 0.076	7.315 ± 0.071
7.2 ± 3.6**	9.0 ± 4.1**	7.6 ± 3.3**	6.4 ± 3.2**
12.0 ± 2.9	11.3 ± 3.4*	11.5 ± 2.8	11.7 ± 2.7
60.5 ± 14.8*	53.8 ± 15.8**	58.2 ± 14.0*	62.6 ± 15.0**
5.0 ± 36.7*	7.8 ± 40.5	2.5 ± 40.0**	-7.1 ± 36.2

was further reduced by increasing the O₂ content from 40% (C) to 100% (D). There was a tendency for myocardial contractile force to recover when the O₂ was decreased from 100% (D) to 40% (E) and again when the experimental animal was returned to room air (F). ST-segment elevation on the epicardial ECG, caused by the coronary artery constriction, was markedly reduced through 40% O₂ inhalation and even further reduced through 100% O₂. Coronary venous O₂ saturation was markedly decreased by coronary artery constriction indicating that the myocardium being perfused by the constricted artery had become ischemic. Forty percent O₂ inhalation caused a significant increase in this value suggesting that the myocardial ischemia had been ameliorated. This change was even more marked under 100% O₂. Coronary venous O₂ saturation almost returned to the control value. This phenomenon was reproduced inversely by changing from 100% (D) back to 40% O₂ (E) and to room air (F). Changes in myocardial O₂ extraction mirrored the changes in coronary venous O₂ extraction. The elevation in coronary venous O₂ saturation resulting from increasing the O₂ concentration from air to 40% and then to 100% was accompanied by a decrease in myocardial O₂ extraction. This indicated that the perfused myocardium had become more aerobic. Due to the coronary artery constriction, myocardial lactate extraction rates showed changes similar to those found for coronary venous O₂ saturation,

Fig. 3. Changes in electrocardiogram, coronary venous O₂ saturation, myocardial O₂ extraction and lactate extraction.

* $p < 0.05$; ** $p < 0.01$ against each preceding value.

from utilization ($28.0 \pm 16.4\%$ at A) to production ($-0.9 \pm 36.9\%$ at B). This suggests coronary artery constriction is effective in producing myocardial ischemia. Myocardial lactate production shifted back to utilization during O₂ inhalation, the value at 100% O₂ ($7.8 \pm 40.5\%$) being greater than that at 40% O₂ (5.0 ± 36.7 at C and $2.5 \pm 40.0\%$ at E), again indicating that the myocardium becomes more aerobic during O₂ inhalation and that 100% O₂ is more effective in that respect than 40% O₂. Although, there was a considerable variation in the measured lactate values, this phenomenon was also reproduced inversely (from D to F).

DISCUSSION

Coronary artery constriction caused an elevation in the ST-segment on the epicardial ECG, a decrease in myocardial contractile force, a decrease in coronary venous O₂ saturation and a change towards production of myocardial lactate; all suggesting that reduction in coronary flow through constriction causes myocardial ischemia. These ischemic changes were considerably reversed by 40% O₂ inhalation and even more markedly so through 100% O₂ inhalation. The beneficial effects of O₂ (shown from B to D) were inversely reproduced from D to F indicating that these effects are not time course dependent.

Maroko et al. (1975), reported that administration of 0.40 FIO₂ following an experimental coronary artery constriction decreased epicardial ST-segment elevation as well as preserved creatine phosphokinase activity (CPK). This reflected a reduction in ischemic injury. Administration of 1.0 FIO₂, however, did not lead to any further decrease. Unfortunately, this conclusion was based only on changes in epicardial ST-segments and whether there is a further preservation of CPK activity thanks to 1.0 FIO₂ or not has never been studied. Although ECG ST-segment change are clinically useful, the correlation between epicardial ST-segments and the extent of the myocardial infarction or regional myocardial blood flow is poor (Irvin and Cobb 1977). Fozzard and DasGupta (1976) postulated that interpretations made from the extent or magnitude of ST-segment changes overlying the area of ischemia may be misleading and that ST-segment mapping should not be used as an independent measure of ischemia. The present study also indicates that the beneficial effects of increasing O₂ concentration from 40% (C) to 100% (D) were not evidenced by measurements of epicardial ST-segment change. However, the superiority of 100% O₂ over 40% O₂ is evident if the beneficial effects of its inhalation upon coronary venous O₂ saturation, on myocardial O₂ extraction, and myocardial lactate utilization are taken into account. Inhalation of 100% O₂ for 24 hr has been reported as causing no toxicity (Singer et al. 1970) but other reports have indicated that breathing more than 95% O₂ caused a significant alveolar-capillary leak after 17 hr, even though these changes were reversible (Davis et al. 1983). During the relatively short period of the acute phase, during the treatment of acute myocardial ischemia takes precedence over all other actions, 100% O₂ breathing should be recommended for all patients just as long as O₂ toxicity does not appear. Several studies have indicated that O₂ inhalation may not result in such beneficial effects. Sayen et al. (1951) inserted electrodes into the center of the ischemic myocardium in dogs after complete occlusion of the coronary artery. Readings of myocardial O₂ tension following 100% O₂ breathing indicated only a small increase (from 12 to 17). Rawles and Kenmure (1976) divided 157 patients with acute myocardial infarction into air and O₂ groups and found no significant differences in mortality rates. At the same time, numerous studies have indicated that the effects of O₂ inhalation on myocardial ischemia are also beneficial. The experimental results by Maroko et al. (1975) were confirmed in a coronary care unit in 17 patients with acute anterior transmural infarction by Madias et al. (1976). Ganz et al. (1972) proved in both clinical patients and in dogs (Ishikawa et al. 1974b) that following O₂ inhalation regional myocardial lactate utilization was improved in spite of a reduction in coronary flow. Thurston et al. (1973) conducted a randomized, controlled clinical trial with a large number of patients (208) with recent acute myocardial infarction. They concluded that the mortality rate for patients treated with O₂ was significantly reduced in comparison with that of the controls (16.5 vs 22.9%). In particular, they found that the mortality rate for high-risk groups may have been

reduced by O₂ to about half. Ashfield and Gavey (1969) came to a similar conclusion using 40 patients with acute myocardial infarction. They found that O₂ was beneficial in the more severe cases: the worse the pain the more O₂ seemed to help. Dyspnea was also improved and similar benefits were shown for arrhythmias.

A possible block to greater utilization of O₂ therapy is that a number of simple questions are still left unanswered. Eckenhoff et al. (1947), as early as 1947, noted an 11% reduction in coronary blood flow resulting from 100% O₂ breathing in dogs. Also, Sobol et al. (1962) demonstrated that while 100% O₂ inhalation caused a 16% increase in arterial O₂ content, it was accompanied by a 22% reduction in coronary blood flow, thereby creating an overall reduction in myocardial O₂ delivery. An experimental study on dogs demonstrated that coronary flow under partial occlusion of the artery was even further reduced under 100% O₂ breathing (Ishikawa et al. 1974b). Lammerant et al. (1969) came to the conclusion that elevation of arterial Po₂ exerted a direct constrictive action on the coronary vessels. Gilmour et al. (1973) reported a decrease in cardiac output following O₂ inhalation in experimental dogs with acute myocardial infarction. However, this reduction in cardiac output in patients with myocardial ischemia may be beneficial in protecting the acutely ischemic myocardium.

Even though O₂ delivery is not increased by O₂ breathing, if a more pronounced reduction in myocardial O₂ consumption which outweighs the reduction in O₂ delivery supervenes, the net effect will be beneficial to the ischemic myocardium. The fact that O₂ breathing reduces myocardial contractile force has been shown repeatedly in experimental animals (Ishikawa et al. 1974b) as well as in clinical patients with ischemic myocardium (Ishikawa et al. 1974c), although effects of O₂ on myocardial contractile force is rather complicated (Ishikawa et al. 1983). Since myocardial contractile force is one of the major determinants of myocardial O₂ consumption (Sonnenblick et al. 1968), a decrease in myocardial contractile force in the ischemic myocardium will also reduce myocardial ischemia. Left ventricular wall tension is also one of the major determinants of myocardial O₂ consumption (Sonnenblick et al. 1968). Since left ventricular tension parallels left ventricular chamber size, a reduction in left ventricular size will cause a reduction in myocardial O₂ consumption. Although left ventricular size was not measured in the present study, our previous studies with open-chest dogs (Ishikawa et al. 1982) and in clinical patients (Ishikawa et al. 1984) indicated consistent reductions of approximately 1 to 3% in left ventricular segment length. It is now evident that O₂ inhalation causes a lower heart rate, a smaller contractile force and a smaller heart chamber size. These, in combination, bring an oxygen-sparing effect to the ischemic myocardium just as beta-blocking agents are effective to the ischemic myocardium because those agents reduce myocardial O₂ consumption.

It has been shown that exposure to hypoxia increase the activity of the

sympathetic nervous system and the adrenal medulla (Woods and Richardson 1959). In hyperoxia, on the contrary, urinary or blood catecholamine decreases in normal subjects (Hale et al. 1964) as well as in patients with pulmonary hypertension (Haneda et al. 1983). These neurohumoral effects which result from oxygen breathing are also beneficial that they reduce myocardial oxygen consumption.

The beneficial effects of 40% and 100% O₂ inhalation were shown in the acutely-ischemic but probably not infarcted myocardium in the present study. It may be difficult to translate the present results directly to the clinical patients with acute myocardial infarction. However, the present experimental model has some similarity to the very acute stage of myocardial infarction in which the myocardial ischemia is still reversible, to such a myocardium where the supplying coronary artery is severely occluded but not completely occluded or to the remnant viable myocardium which is usually present in the infarcted myocardium. The usefulness of O₂ inhalation to such an acutely-ischemic myocardium was shown in this study.

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