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INFLUENCE OF HYPERBARIC OXYGENATION ON CORONARY ARTERY EMBOLIZATION IN DOGS

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ABSTRACT

The effects of hyperbaric oxygenation were investigated in 46 dogs with myocardial infarction produced by injecting microspheres of 40 μ in diameter.

1) Hyperbaric oxygenation did not prevent early death from ventricular fibrillation. However, it afforded protection against late death.

2) The hemodynamic deterioration of myocardial infarction was prevented by hyperbaric condition.

3) Ventricular tachycardia and ventricular ectopic beats occurred more frequently in hyperbaric condition than in room air.

4) The deviation of the ST segment was reduced by hyperbaric oxygenation.

5) SGOT and SGPT were not significantly reduced by hyperbaric oxygenation.

6) The extent of the infarcted lesion was significantly less in the caisson group than in the control group. Histological findings at the margin of the lesion showed further regenerative improvement in the caisson group.

7) Microangiographic studies showed that revascularization was developed more progressively in the caisson group.

The results suggested the protective effect of hyperbaric oxygenation on the ischemic process after myocardial infarction.

With the present study, it would be concluded that hyperbaric oxygenation exerts a beneficial effect on myocardial infarction.

INTRODUCTION

Hyperbaric oxygenation has been reported to be beneficial in a variety of ischemic situation. Theoretical considerations suggest that hyperbaric oxygenation may limit the extent of myocardial lesion and reduce the mortality. The previous studies of hyperbaric oxygenation in myocardial infarction will be classified as follows.

Smith and Lawson[1] reported that the administration of oxygen under high pressure reduced the mortality following ligation of the circumflex branch of the left coronary artery in dogs. Similar studies have been reported by Illing-

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worth[2], Meijne[3)4)] and many other investigators[5)18)].

Jacobson[19)20)] reported the studies of hyperbaric oxygenation on acute diffuse myocardial infarction in dogs produced by embolization of microspheres into the coronary arteries. Kuhn[21)22)], Holloway[23)] and Peter[24)] reported the evaluation of hyperbaric oxygenation on acute diffuse myocardial infarction.

Cameron[25)-28)] reported the clinical trial in the patients treated in a hyperbaric chamber designed to operate at a pressure of two atmospheres absolute (2 ATA). Similar observations have been reported by Moon[29)].

It is acceptable that hyperbaric oxygenation reduces the mortality and protects the ischemic lesion of myocardial infarction, because partial pressure of oxygen dissolved in the capillary blood is high. The arterial PO_2 rises to 2200 mmHg in 100 per cent oxygen inhalation at three atmospheres absolute (3 ATA), and the amount of oxygen physically dissolved in the blood plasma rises from 0.3 volume per cent while breathing room air to 6 volume per cent while breathing 100 per cent oxygen at 3 ATA.

Various opinions have been reported previously on hyperbaric oxygenation for myocardial infarction. Their interests attached to the influence of hyperbaric oxygenation on the mortality, hemodynamics, ECG findings, SGOT, SGPT and histological findings of the lesions. Further studies on these problems are necessary.

It is the purpose of the present study to justify the influence of hyperbaric oxyenation on these problems concerning embolization of the coronary arteries in dogs.

MATERIALS AND METHODS

First stage experiment: Dogs weighing between 10 and 15 kg were anesthetized with intraabdominal injection of thiopental sodium in a dose of 30 mg per kg of body weight. After the induction of anesthesia, a cardiac catheter sized of 7F was inserted into the ascending aorta through the exposed left carotid artery. The catheter was then guided into the left coronary artery under X ray fluoroscopy and was wedged into the left circumflex or the left anterior descending artery. Microspheres of clubmoss spores (hycopodium), 40 μ in diameter, were injected at a dosage of 0.25 mg per kg body weight.

According to the abovementioned technique, acute myocardial infarction was produced in 30 dogs. ECG findings after embolization revealed the elevation of the ST segment. These dogs were divided at random into two groups; half of them were prepared as the caisson group and maintained in 100 per cent oxygen at 3 ATA for 2 hours daily for a week under a continuous observation through a window of the chamber.

The remainders were served as the control group and kept outside breathing

room air at normal atmospheric pressure.

Continuous monitoring of ECG was performed in Leads II and aVF in both groups. Arterial pressure was recorded continuously through a catheter placed into the femoral artery. Blood samples were drawn for SGOT and SGPT determination at regular intervals, as shown in Table 6. All animals were followed until their death or slaughter after a month. The pathological examinations were performed following death or at the time of slaughter.

TABLE 1. Numbers of experimental animals

Experiment	Numbers of experimental animals		
	Caisson group	Control group	Total
1st stage exp. (for mortality rate)	15	15	30
2nd stage exp. (for pathological studies)	8	8	46

Second stage experiment: For investigation of the pathological changes, following additional studies were performed. Eight animals were prepared as the caisson group and were sacrificed after 3, 5, 7 and 10 days'survival. Eight control dogs were prepared and sacrificed after the same day's survival. Each heart was investigated macroscopically and microscopically.

Microangiography: Microangiographic studies were performed in hearts of all animals. As soon as feasible after examination of gross appearance on removed heart by autopsy, microangiography was performed by the following method.

A small polyethlen catheter was inserted into one of the main arteries supplying the lesion, usually into the left anterior descending artery or the left circumflex artery. Through the catheter, heparinized saline solution was perfused to wash out the blood from the capillaries and the veins.

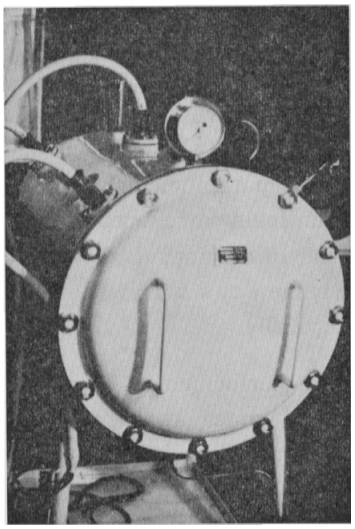
The opaque material used for microangiography was a thin barium soluion. The material was injected into the coronary vessels through the catheter under controlled pressure by hand. The pressure varied from 150 to 200 mmHg, but never exceeded this range. The injection to the specimen was considered to be completed when the veins were filled by the opaque material. After the complete filling of the material in the specimen, ligatures were placed on the open vein, and the specimen was fixed in a 10 per cent buffered formalin solution.

After 10 or 15 days' fixation, the specimen was sliced in 3 mm thick at

the center of the region. These slices were ranged on a X ray film, and rentogenography was made with Sakura Konilitho Contact Film. An industrial X ray unit (Softex EMB type) was used and exposuring conditions were as follows: 24 kV, 2.5 mA, at 37.5 cm distance, with an average exposure of 8 minuts. The film was processed for 5 minutes in a X ray developing solution, Cleadol by Konishiroku Photo Ind. Co. LTD. and then, placed in a fixer for 10 minutes.

They were observed with the naked eye and with a standard microscope. The comparative studies were made between both groups at each period.

Apparatus and method for hyperbaric oxygenation: The hyperbaric chamber used was developed in this department by Sakaibara and others, and its dimentions are 650 mm in diameter and 1115 mm in length, as shown in Fig. 1.



The chamber can be ventilated by means of 4 valves. Through two windows, 100 mm in diameter, the inside of the chamber can be observed. Three cables are passed into the chamber, each containing 12 leads, and ECG can be monitored through these leads. The chamber also incorporates safety valves, thermometers and pressure gauges.

Before 2 ATA was attained, oxygen was insufflated with one valve half open, in order to replace fully the air in the chamber. Fifteen minutes was necessary before the internal pressure reached 3 ATA.

FIG. 1. Hyperbaric chamber developed by Sakakibara; 650 mm in diameter and 1115 mm in length.

At 3 ATA, it was maintained for 2 hours and then decompressed to the atmospheric pressure, taking 15 minutes from 3 ATA. These procedures were performed in experimental animals once a day.

RESULTS

Mortality: Mortality was investigated in 15 dogs of the caisson group and 15 control dogs. The mortality in both groups is illustrated in Table 2.

Rate of the caisson group was 33.3 per cent within 24 hours. In the control group, 20.0 per cent of the animals died within 24 hours. These animals died from ventricular fibrillation or cardiac arrest.

TABLE 2. Numbers of death and mortality rate

Time after embolization	Numbers of death and mortality rate			
	Caisson group		Control group	
	Numbers	%	Numbers	%
Within 24 h	5	33.3	3	20.0
24 h ~ 3 days	3	20.0	2	13.3
3 days ~ 5 days	2	13.3	4	26.6
5 days ~ 7 days	1	6.6	4	26.6
7 days ~ 10 days	0	0	1	6.6
10 days ~ 30 days	4	26.6	1	6.6
Total	15	100	15	100

The dogs died within 15 minutes after embolization were excluded, because the cause of death seemed to be a shock state during the embolization procedure. The mortality from 24 hours to 3 days in the caisson group and control group was 20.0 per cent and 13.3 per cent, respectively. The mortality between 5 and 10 days significantly decreased in the caisson group than in the contol group.

Thirty days' survival rate was higher in the caisson group than in the control group. The mortality after 10 days was considerably less in both groups.

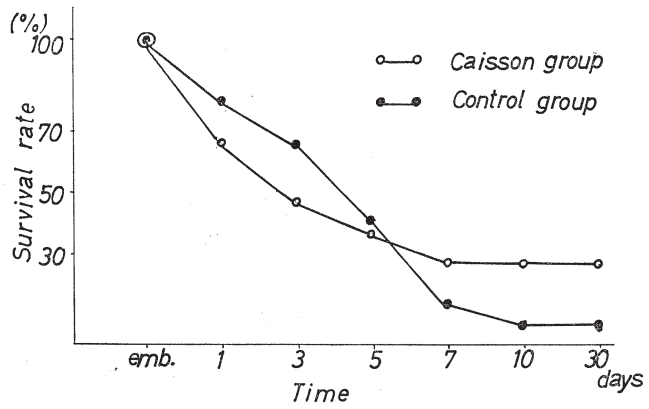


FIG. 2. Survival rate in the 1st stage experiment.

In this experiment, early death following coronary embolization was due

to ventricular fibrillation, and late death was due to ventricular fibrillation, cardiogenic shock, serious arrhythmias and especially heart failure originated in ischemic myocardial lesion.

Cardiac rate: The alteration of cardiac rate is presented in Table 3.

Fifteen animals in the caisson group and 15 control dogs were measured for 6 hours after embolization at regular intervals. The cardiac rate in all animals was increased at the moment of embolization. The caisson group after one hour showed the change of cardiac rate in 9 of 15 animals; the decrease more than 5 per minute from the rate at the beginning of the treatment was observed in 7 animals, and increased in the same rate in 2 animals.

In the caisson group after 2 hours at 3 ATA, the rate was decreased in 9 animals, increased in one and unchanged in 5. After decompression, the rate was decreased in 6 animals, increased in 2 and unchanged in 7. The rate of 3 hours after decompression was decreased in 7 animals, increased in 2 and unchanged in 6. The rate in the control group indicated a slight decrease within 6 hours after embolization.

As a general rule, in the caisson group the cardiac rate showed a decreasing tendency in hyperbaric condition, but the tendency was reversible when animals were removed from this condition.

TABLE 3. Changes of cardiac rate

Caisson group					Control group				
Time after emb.	Numbers			Average rate	Time after emb.	Numbers			Average rate
	Decrease	Increase	Unchange			Decrease	Increase	Unchange	
15 m.	—	—	—	142	15 m.	—	—	—	144
1 h. 30 m. (1 h. at 3 ATA)	7	2	6	124	1 h. 30 m.	2	3	10	141
2 h. 30 m. (2 h. at 3 ATA)	9	1	5	113	2 h. 30 m.	3	5	7	135
2 h. 45 m. (after decomp)	6	2	7	136	2 h. 45 m.	4	4	7	134
6 h.	7	2	6	123	6 h.	6	3	6	131

Arterial pressure: The arterial pressure revealed a tendency to fall at the moment of embolization. The degree of the decrease in both groups, however, did not indicated a so significant difference within 15 mintes after embolization.

After the treatment for one hour at 3 ATA, the arterial pressure in the caisson group increased more than 10 mmHg in 6 of 15 animals as compared

with the value at the beginning of the treatment, decreased in 3 animals, and was unchanged in 6.

After 2 hours at 3 ATA, average pressure was 136 mmHg, and the pre-

TABLE 4. Changes of arterial pressure

Caisson group					Control group				
Time after emb.	Numbers			Average pres. (mm Hg)	Time after emb.	Numbers			Average pres. (mm Hg)
	Increase	Decrease	Unchange			Increase	Decrease	Unchange	
15 m.	—	—	—	82	15 m.	—	—	—	78
1 h. at 3 ATA	6	3	6	125	1 h. 30 m.	3	6	6	94
2 h. at 3 ATA	7	3	5	136	2 h. 30 m.	5	3	7	107
After decomp.	5	4	6	89	2 h. 45 m.	5	3	7	107
6 h.	6	3	6	108	6 h.	6	3	6	112

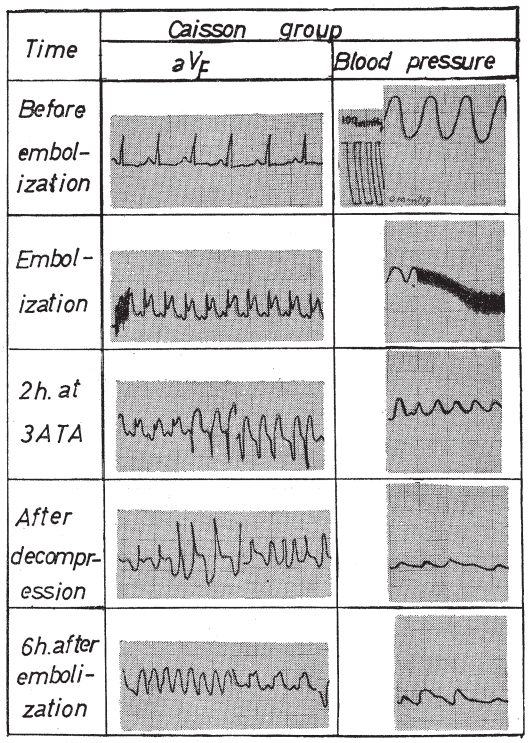


FIG. 3. Changes of arterial pressure, showing elevation in hyperbaric conditien, and returning to the level pretreatment after decompression.

ssure increased in 7 animals, decreased in 3 and unchanged in 5.

After decompression, the pressure fall, and the average pressure was 89 mmHg, as shown in Table 4. Occasionally, arterial pressure in some cases remained at a lower level than before the treatment.

The average pressure in the control group showed an elevation from 78 mmHg to 112 mmHg within 6 hours after embolization.

ECG findings: Before embolization, slight arrhythmias were found in a few animals, and they were considered to be due to anesthetic agent.

In 6 animals ventricular fibrillation occurred within several minutes after embolization, and developed to death in all instances. These animals died within 15 minutes after embolization were excluded from this experiment.

The death in the first 24 hours was encountered in 5 animals of the caisson group. No death nor occurence of ventricular fibrillation was observed in the period when the animals were exposed to oxygen in the chamber. Ventricular fibrillation occurred frequently in the period after the animals were removed from hyperbaric oxygenation to room air.

Fatal ventricular fibrillation occurred in 3 of 15 control animals within the

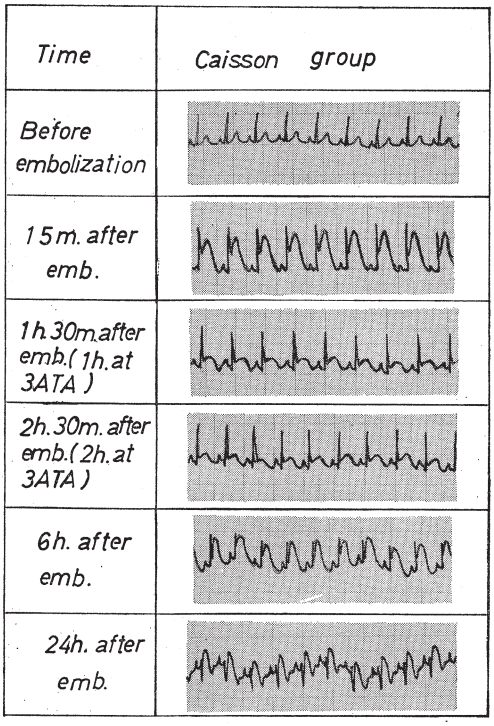


FIG. 4. Changes of ST segment, showing improvement by hyperbaric oxygenation.

first 24 hours. The results indicated a tendency of occurrence of early ventricular fibrillation in the caisson group in this experiment.

The degree of ST elevation in aVF in the caisson group was compared with that of the control group. In the caisson group, the reduction of ST elevation was seen in 5 animals after one hour at 3 ATA. However, constant ST elevation remained in 10 animals.

After 2 hours at 3 ATA, ST elevation in 7 animals was reduced as much as 0.1 mV comparing with the level of 15 minutes after embolization. During the treatment at 3 ATA of oxygen in 8 animals ST elevation was unchanged. However, after 2 hours at 3 ATA, maximum improvement in average change of ST elevation was encountered and the value was 0.26 mV.

In general, after decompession, ST elevation was improved in 4 animals compared with 15 minutes after embolization, and unchanged in 6 animals.

In the caisson group, 6 hours after embolization ST elevation was seen to be improved in 6 animals, unchanged in 7 and increased in 2.

In the control animals, deviation of ST segment was found to decrease in 6 animals, to increase in one, and to be unchanged in 8. In the most cases, ST deviation was reduced gradually for a week. However, ST elevation in the course of survival was reduced rapidly in the caisson group.

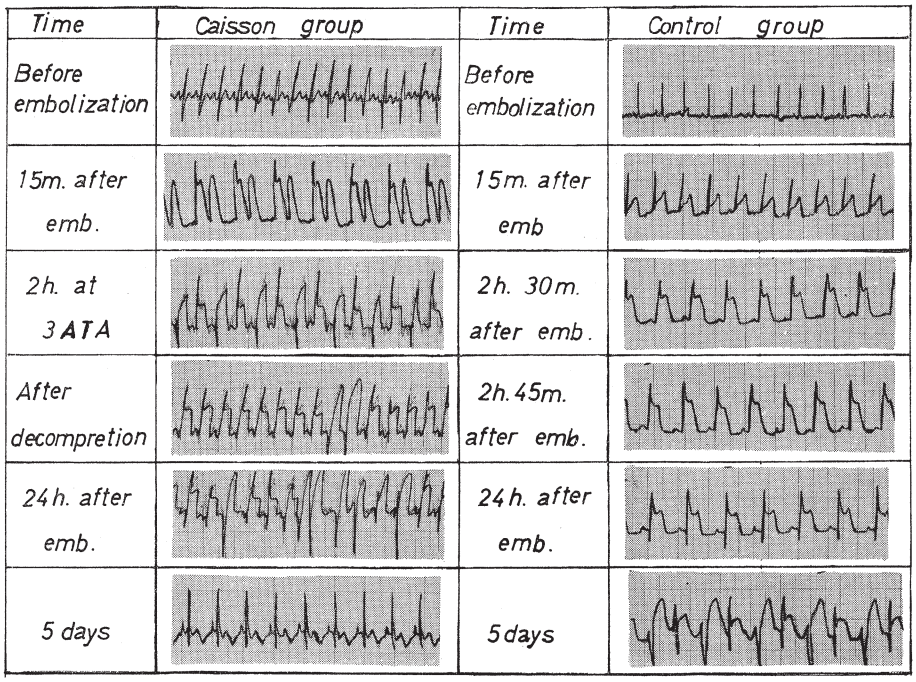


FIG. 5. Changes of ECG findings in the course of survival.

TABLE 5. Changes of ST elevation

Caisson group					Control group				
Time after embolization	Numbers			Averagech-ange (mV)	Time after embolization	Numbers			Averagech-ange (mV)
	Decr-ease	Incr-ease	Unch-ange			Decr-ease	Incr-ease	Unch-ange	
15 m. after emb.	—	—	—	0	15 m. after emb.	—	—	—	0
1 h. 30 m. (1 h. at 3 ATA)	5	0	10	−0.18	1 h. 30 m.	1	1	13	0
2 h. 30 m. (2 h. at 3 ATA)	7	0	8	−0.26	2 h. 30 m.	3	4	8	+0.05
2 h. 45 m. (after decomp)	4	5	6	+0.06	2 h. 45 m.	4	2	9	−0.04
6 h.	6	2	7	−0.08	6 h.	6	1	8	−0.06

Some types of arrhythmia were observed in some occasion after embolization. These arrhythmias included frequent ventricular ectopic beats, short duration of ventricular tachycardia, supraventricular ectopic beats, nodal rhythm and the first or second degree of heart block.

Ventricular ectopic beats and vemtricular tachycardia were observed fre-

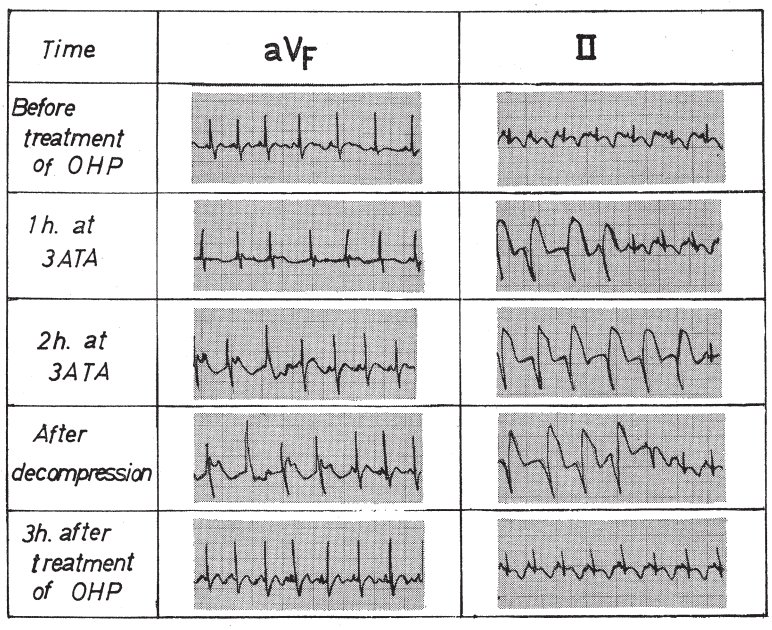


FIG. 6. Frequent occurrence of ventricular premature beats in hyperbaric oxygenation.

quently in 9 animals of the caisson group and in 7 animals in the control group. These arrhythmias frequently occurred in hyperbaric condition, and they always disappeared when animals were removed from hyperbaric condition. (Fig. 6)

The other types of arrhythmia were observed in few cases; nodal rhythm occurred temporarily in 2 animals after embolization, and the second degree of heart block was observed in one animal of the control group. Auricular fibrillation and other arrhythmias did not occur. There was no significant difference in the occurrence of nodal rhythm and heart block between both groups.

The Q wave was found in aVF of the animals survived over 5 or 10 days after embolization. The Q wave revealed no remarkable changes in hyperbaric condition, and no significant difference between both groups.

SGOT anb SGPT: SGOT and SGPT were investigated in each animals of both groups, which were survived for 5 days. Blood samples were drawn at regular intervals.

SGOT and SGPT levels at the start of the experiment were found within normal limits in all animals. The average value in 15 minutes after embolization was within normal limits.

By 3 hours after embolization in both groups, the values indicated a tendency of slight elevation. SGOT and SGPT 12 hours after embolization indicated a rapid elevation: 214 and 136 units in the caisson group, and 198 and 164 in the control group, respectively.

SGOT and SGPT after 24 hours revealed the maximum values: 256 and 212 in the caisson group, and, 254 and 133 in the control group.

By 3 days after embolization, the values were reduced to 121 and 93 in the caisson group, and, 143 and 118 in the control group. Five days after embolization the values were reduced further.

The results indicated that there was no significant difference in the average values between both groups in the course of elevation to the maximum value. The maximum value revealed rather higher in the caisson group than in the control group. However, the value after 3 days in the caisson group was reduced more rapidly than in the control group. (Table 6)

In order to evaluate the influence of hyperbaric oxygenation on the transaminase level, SGOT and SGPT in animals without embolization procedure and exposed to 100 per cent oxygen at 3 ATA for 2 hours were investigated.

The values showed a rise at the end of 6 hours with an average rise to 59 and 33, and reached a peak at the end of 24 hours with an average rise to 76 and 42. Then, the value was followed by a decline to the near normal level at the end of 3 days.

TABLE 6. Changes of SGOT and SGPT

Time after embolization	Average values of SGOT and SGPT (Unit)			
	Caisson group		Control group	
	SGOT	SGPT	SGOT	SGPT
Pre. emb.	24	22	28	22
15 m.	26	24	27	24
3 h.	48	24	43	20
12 h.	214	136	198	164
24 h.	256	212	254	133
3 days	121	93	143	118
4 days	108	85	110	98
5 days	81	42	99	54

Macroscoic observation of cardiac lesion: The hearts were examined grossly in each animal. Their hearts were classified into two groups according to the location of the infarcted lesion; in 65.2 per cent, the lesion was found in the distribution of the left anterior descending artery, and in the remainders, in the distribution of the left circumflex artery. The hearts of the animals died within 24 hours after embolization revealed no signicant difference in the extent of the lesion between both groups.

The lesion of survivals over 2 days showed a change of dark hemorrhagic discoloration, that is a purplish area with brownish mottle on the epicardium. The diameter of the area was measured and presented in Table 7 and Fig. 7.

The extent of the lesion 3 days after embolization revealed no appreciable difference between both groups. The size of the lesion 5 or 10 days after

TABLE 7. Extent of lesion

Experiment	Group	Numbers of dogs	Extent of lesion (cm) (diameter of lesion)		
			Less than 4 (cm)	4-6 (cm)	6-8 (cm)
1st stage exp.	Caisson group	11	1	8	2
	Control group	12	2	7	3
2nd stage exp.	Caisson group	8	3	5	0
	Control group	8	1	5	2

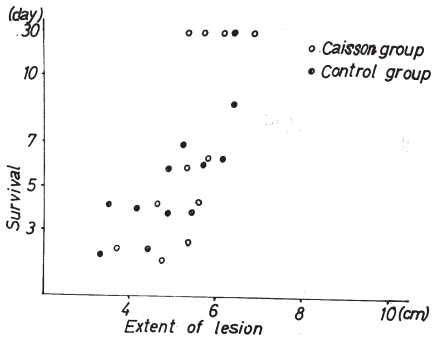


FIG. 7. Extent of lesion, showing less extent of lession in the caisson group than in the control group.

embolization indicated a tendency of a less extent in the caisson group as compared with in the control group.

Colour of the surface of the lesion observed in the control group was darker than that in the caison group.

Particularly, cut surface of the lesion showed more dark brownish in colour in the control group. (Fig. 8, 9)

In 30 days' survival animals, scar formation was found in the lesion. There was no significant difference in the extent and degree of the lesion between both groups.

Histological findings: The findings of the animals died within 24 hours after embolization revealed multiple occlusions in the small coronary arteries by microemboli of clubmoss spores which were found as yellow microspheres. In the lesion, intramural hemorrhage in the wall of the arteries was discovered.

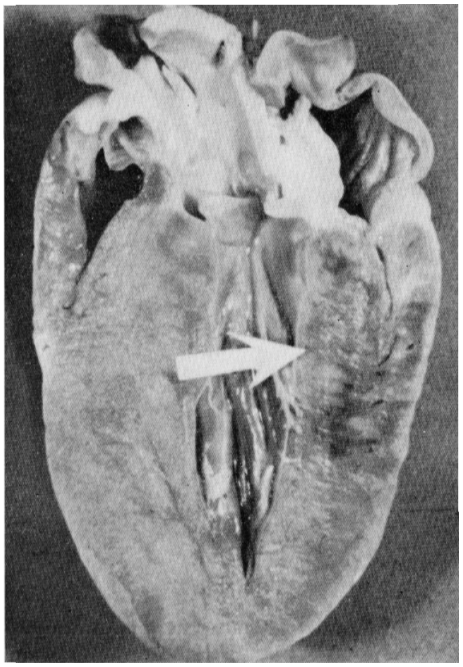


FIG. 8. The lesion in the caisson group 10 days after embolization, showing less extent of lesion in the caisson group.

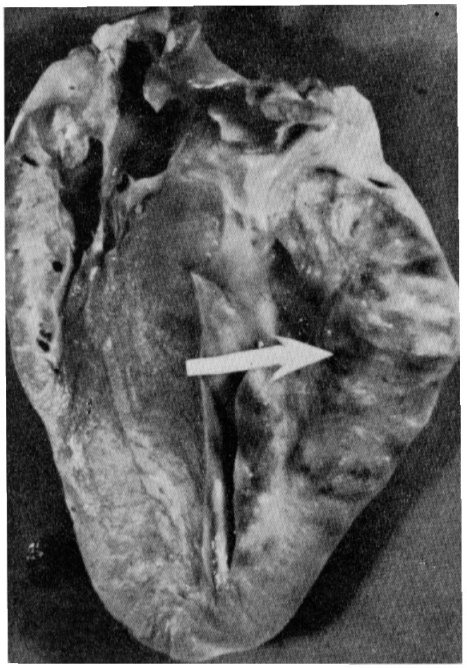


FIG. 9. The lesion in the control group 10 days after embolization, showing much extent of the lesion in the control group.

However, no degenerative or necrotic change of muscle fibers was found. Further no difference between both groups was observed. (Fig. 10, 11)

In the control animals slaughtered 3 and 5 days after embolization, the

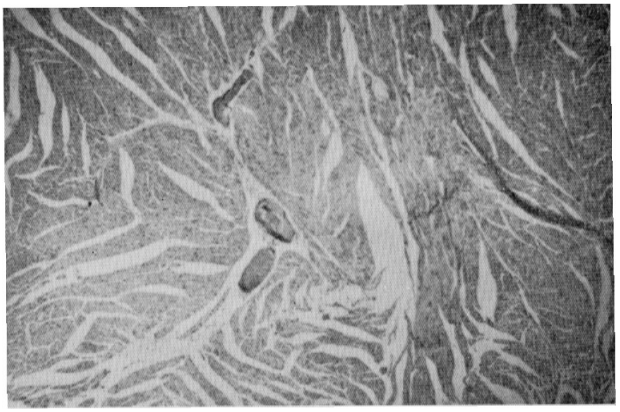


FIG. 10. Histological findings in the caisson group within 24 hours after embolization, showing multiple occlusions in the small coronary arteries by microemboli of clubmoss spores. (×100. hematoxilin-eosin)

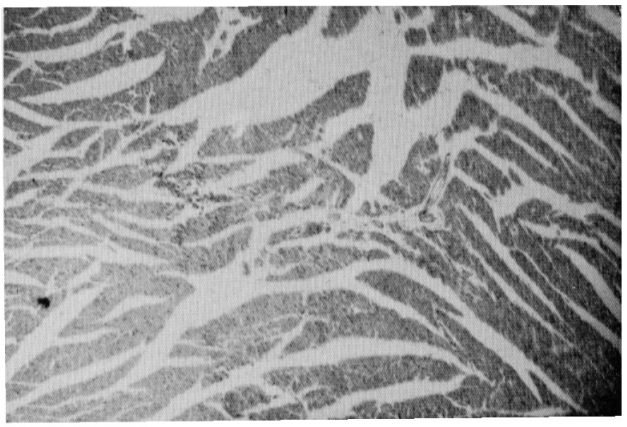


FIG. 11. Histological finding in the control group within 24 hours after embolization, showing no degenerative change of muscle fibers and no difference between both groups. (×100. hematoxilin-eosin)

lession was composed of brick-red muscle fiber by hyaline degeneration with cross striation and the divided nuclei.

At the margin of the lesion, infiltration of a large number of polymorphonuclear leucocytes was observed in interstitial spaces. In contrast with the findings in the control group, lesion in the caisson group revealed the similar degenerative changes of muscle fibers. It indicated, however, a tendency of less extent of the area infiltrated by polymorphonuclear leucocytes. (Fig. 12, 13)

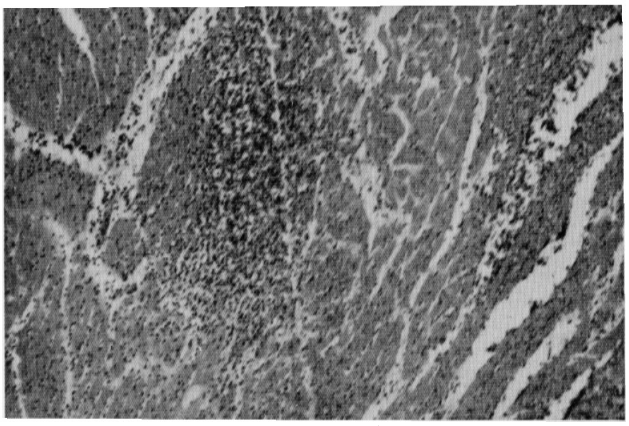


FIG. 12. Histological finding in the caisson group 5 days after embolization, showing less extent of the area infiltrated by leucocytes in the caisson group. (×100,hematoxillin-eosin)

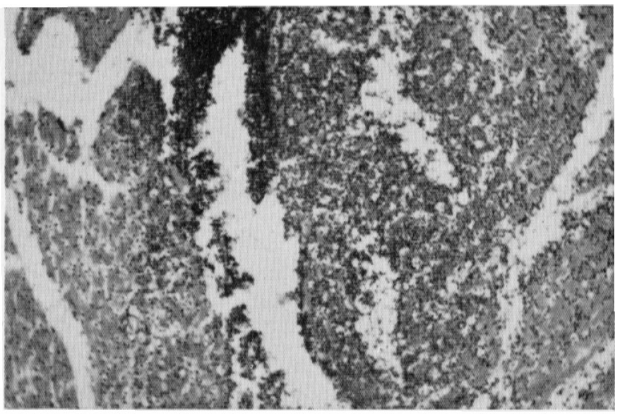


FIG. 13. Histological finding in the control group 5 days after embolization, showing a tendency of much extent of the area infiltrated by leucocytes in the control group as compared with in the caisson group. (×100. hemdtoxillin-eosin)

In the control group sacrificed 7 and 10 days after embolization, the lesion was composed of necrotic muscle fibers and leucocytic infiltration, and these changes became more progressive with time. The necrotic tissue at the margin of the infarcted area remained, and then regenerative changes were not developed.

In contrast to the abovmentioned changes, the lesion in the caisson group indicated the existence of the similar infiltration and necrotic destruction of muscle fibers. However, regenerative changes by granulation tissue were de-

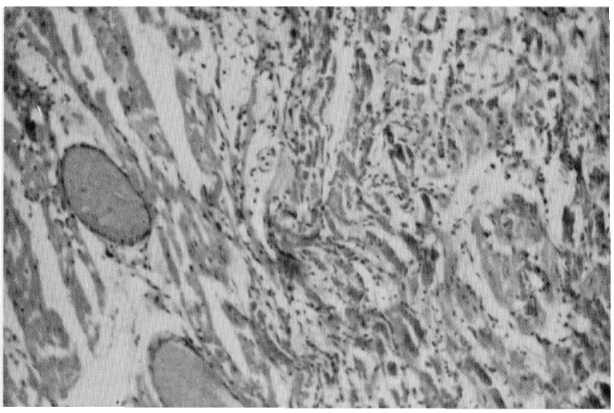


FIG. 14. Histological alterations in the caisson group 10 days after embolization, showing further regenerative improvement in the caisson group than in the control group. (×100. hematoxillin-eosin)

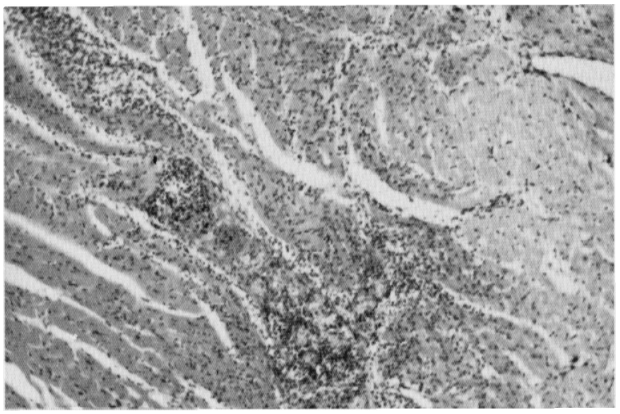


FIG. 15. Histological changes in the control group 10 days after embolization, showing remained leucocytic infiltration and necrotic muscle fibers. (×100. hematoxilin-eosin)

veloped more progressively at the margin of the lesion than in the control group.

In the animals sacrificed 30 days after embolization, the lesion was replaced by connective tissue and scar formation. These findings indicated no difference between both groups.

Mictoangiography: Microangiographic findings within 24 hours showed arterial occlusion in the small arteries, and the infarcted area was found as a poor vascular lesion. However, there was no remarkable difference in the extent of the region between both groups.

In animals survived less than 5 days, no significant difference in the extent of the lession between both groups was observed.

On the contrary, the findings in animals survived more than 5 days revealed the development of the fine arteries toward the center of the lesion. The revascularity in the lesion was developed more progressively in the caisson group than in the control group.

For determination of the density of distribution of the vessels, the number of arterial branches was counted in each microscopic field at twenty-fold magnification of the lesion, and the results obtained were presented as the average number of arteries in Table 8.

These figures were compared with both groups in each period of survival. The figures were found larger in the caisson group. (Fig. 16～23)

TABLE 8. Numbers of vessels in a microscopic field (×20)

(1st stage experiment)

Time after emb.	Average numbers of vessels	
	Caisson group	Control group
Within 3 days	18	19
3~ 5 days	38	35
5~ 7 days	76	62
7~10 days	~	72

(2nd stage experiment)

Time after emb.	Average numbers of vessels	
	Caisson group	Control group
3 days	22	20
5 days	42	38
7 days	84	65
10 days	143	98

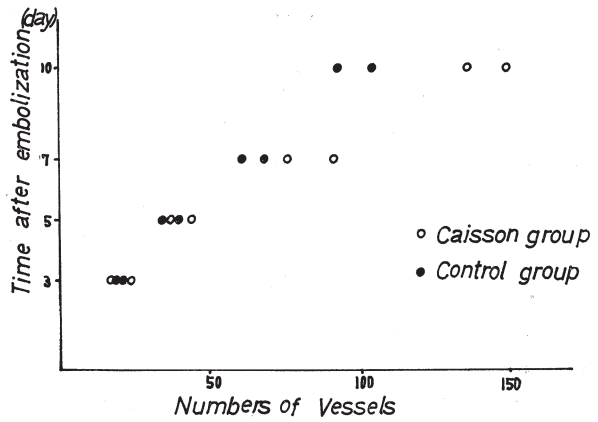


FIG. 16. Numbers of vessels in a microscopic field of micro-angiogram in the second stage experiment.

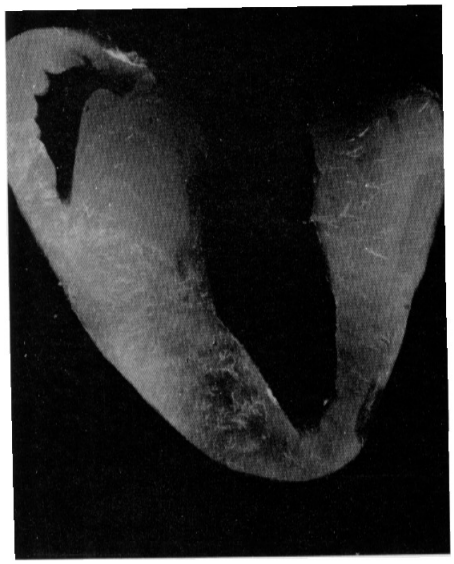


FIG. 17. Microangiogram in the caisson group 5 days after embolization.

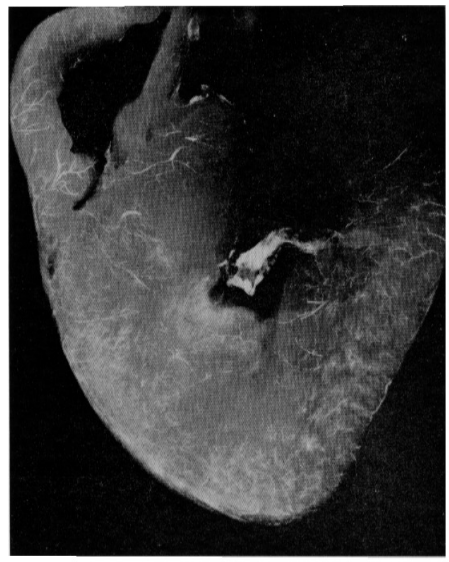


FIG. 19. Microangiogram in the caisson group 10 days after embolization.

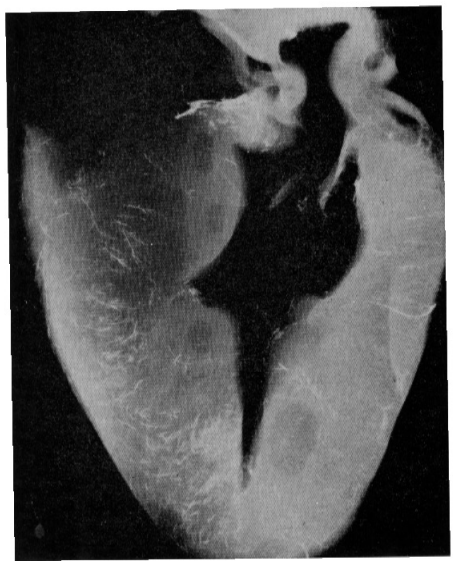


FIG. 18. Microangiogram in the control group 5 days after embolization.

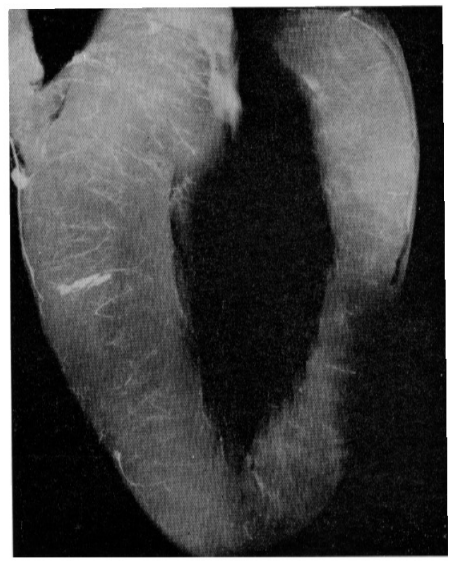


FIG. 20. Microangiogram in the control group 10 days after embolization.

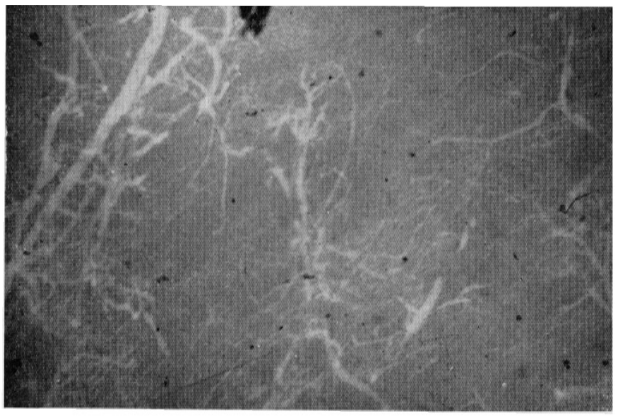


FIG. 21. Microscopic finding of microangiogram in the caisson group 7 day safter embolization (×40.), showing the infarcted area fonnd as a poor vascular region.

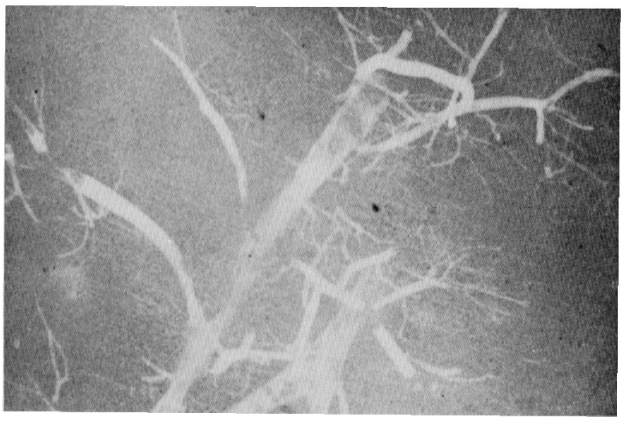


FIG. 22. Microscopic finding of microangiogram in the control group 7 days after embolization (×40.), showing the slight development of fine arteries toward the center of the lesion. No significant difference in the extent of the lesion between both group.

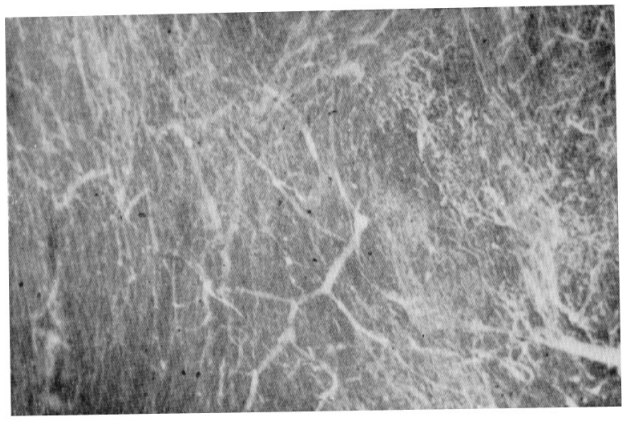


FIG. 23. Microscopic finding of microangiogram in the caisson group 10 days after embolization. Showing more progressive revascularization in the caison group than in the control group.

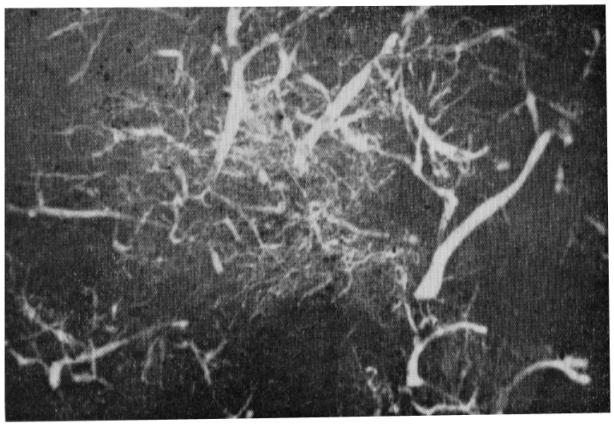


FIG. 24. Microscopic finding of microangiogram in the control group 10 days after embolization. Showing remained poor vascular region of the infarcted area.

DISCUSSION

The effect of hyperbaric oxygenation to change the course of myocardial infarction in men and experimental animals has not been conclusively demonstrated. The results of experimental studies in the literatures suggested that the course of myocardial infarction may be altered by hyperbaric oxygenation.

Mortality: Reports have described the mortality of myocardial infarction. Gazes[30] reported overall mortality of 18.6 per cent among 795 patients after myocardial infarction, and the highest rate of death was shown during the first 4 days.

Mortality reported by Hurwitz[31] was 24 per cent, and that by Day[32] was 18.2 per cent. Julian[33] reported of 31 per cent, and emhasized that the causes of death were ventricular fibrillation, asystole, myocardial rupture, congestive heart failure and cardiogenic shock.

In the experiment of Pifarre[34], the mortality of dogs with the left anterior descending artery ligated was 13 per cent. Chardack[35] reported that 80 per cent of dogs tolerated acute ligation of the artery. Lumb[36] reported that ligation of the left circumflex artery resulted in death in 66 per cent.

There are some investigations on influence of hyperbaric oxygenation on the mortality following myocardial infarction.

Smith and Lawson[1] reported that the pure oxygen at 2 ATA protected the death in dogs after ligation of the circumflex artery.

Roshe and Allen[8] observed the mortality in a method of the left circumflex artery ligation. The rate was 50 per cent in the control group and 30 per cent in the caison group.

In observation by Elk[11][12], mortality in the control group was 100 per cent and 16 per cent in the caisson group. Peter[24] reported almost the same results with embolized pigs.

However, Meijne[4] reported that the mortality showed no difference between both groups of the caisson and control. Holloway[23] compared results of embolized dogs breathing room air, 100 per cent oxygen at 2 ATA or at 3 ATA, and the survival rate was not different in each group.

Cameron[26]-[28] reported that the mortality in the caisson series was high. Five of 7 patients in the treated group died, and 4 of 7 control patients died. The oveall mortality in the first 6 weeks following infarction has been the same in both groups.

The results of Meijne's group, Holloway's group and Cameron's group do not encourage one to conclude the view of the effective protection of hyperbaric oxygenation for myocardial infarction. In spite of these disappointing deduction, results by many other investigations described previously suggest full

significance of the protective effect of hyperbaric oxygenation on death from myocardial infarction.

In the present report, the mortality of both groups within 24 or 48 hours showed no difference. However, the late mortality 3 days after embolization was significantly less in the caisson group than in the control group, and the survival rate for one month indicated to be higher in the caisson group.

The result suggested that there was a different cause between death within 3 days and after 3 days, and the cause of late death was protected by hyperbaric oxygenation.

Cardiac rate and blood pressure: Hemodynamic investigations following myocardial infarction have been performed experimentally after occlusion of the coronary arteries in open chest dogs and with closed method.

Coffman[37] performed hemodynamic investigation in open chest dogs. Mean blood pressure averaged 90 mmHg, and fell by 10 mmHg during occlusion, and then, usually returned to the control level within the first half a minute after release. Heart rate averaged 152 bsats per minute, and rose or fell by 6 to 12 beats during occlusion and after release.

By Kuhn[38) 39)] in the investigation in closed chest dogs with the embolized coronary artery, the average of arterial pressure was recorded to be 143/98 in the preembolized period, and fell to 89/68 after embolization.

Green[40] reported that breathing of 100 per cent oxygen would result in a decrease in coronary blood flow in dogs.

Eckenhoff[41] demonstrated that the arterial pressure fell by breathing of 100 per cent oxygen.

Hahnloser[42] recorded the change of heart rate and arterial pressure in 45 dogs under 100 per cent oxygen inhalation at 4 ATA for 90 minutes. The results showed 15 per cent decrease in cardiac rate and remarkable rhythmic irregularity after one hour of hyperbaric oxygenation, and blood pressure indicated a little fall in about 5 per cent.

The experiment by Petropoulos[10] showed several hemodynamic results after circumflex coronary occlusion in hyperbaric condition. At 3 ATA, the arterial pressure decreased in only 16 per cent of the preocclusive level during the first 5 minutes and one hour after the pressure recovered to the preocclusive level. At 1 ATA, the pressure decreased to 76 per cent of the preocclusive level during the first 5 minutes and one hour after the pressure remained at the same level. The heart rate showed no significant tendency during one hour at 3 ATA and 1 ATA.

In the present experiment, the heart rate in hyperbaric condition indicated a lower level than in room air after embolization in each dog. After decompression, the rate returned to the same level before hyperbaric condition. The

arterial pressure increased in hyperbaric condition after embolization, but after decompression, the pressure decreased to the similar level after embolization before hyperbaric oxygenation. The present report indicated that the hemodynamic condition after embolization was improved only in hyperbaric condition, but the improvements were reversible.

ECG findings: It is acceptable with the evidence that the commonest cause of death following coronary occlusion is ventricular fibrillaticn. With the experimental studies, the evidence was demonstrated by the many workers.

Clinically, ventrirular fibrillation following acute myocardial infarction is thought to be responsible for a great percentage of the sudden death due to coronary arterial disease.

It has been reported by MacLean[43] that acute ligation of the anterior descending artery caused an immediate drop in the ventricular fibrillation threshold.

As described previously, Smith and Lawson[1] reported the protective effect of hyperbaric oxygenation against ventricular fibrillation.

Jacobson and Wang[19,20] reported that the occurrence of ventricular fibrillation was significantly less in dogs exposed to 100 per cent oxygen at 3 ATA after coronary embolization.

These results showed that hyperbaric oxygenation had a powerful effect to protect ventricular fibrillation after myocardial infarction. However, the results by Elk[11,12], and Chardack[9] are less dramatic than the abovementioned reports.

The results of the present study indicated that hyperbaric oxygenation did not reduce the occurrence of death from ventricular fibrillation within 24 or 48 hours after embolization, and then, the mortality was not reduced in the early period of myocardial infarction. These results suggested that administration of hyperbaric oxygenation can afford no protection against ventricular fibrillation which occurs immediately after myocardial infarction.

The same results have been observed by Robertson[8]. In the caisson group of 3 ATA, 13.3 per cent of the animals died from ventricular fibrillation, and in the control group exposed in room air no animal died from ventricular fibrillation. These results are interpreted as supporting the view that the ventricular fibrillation occurred more frequently in hyperbaric oxygenation than in room air. Turnbull[16] investigated on ventricular fibrillation threshold in the control group and in the caisson group at 3 ATA of oxygen, and observed the same results. He emphasized that the threshold was concerned with the blood flow to carry oxygen.

Arrhythmias are routine and serious complications of acute myocardial infarction, and often lead the patients with acute myocardial infarct to death.

Spann[44] observed that in 73 per cent of the patients with myocardial in-

farction, one or more sorts of arrhythmias occurred. Further the rate of the incidence was reported to be 80 per cent by Hurwitz[31], and 90 per cent by Kurland[45].

By these authors, the sort of arrhythmias after myocardial infarction has been considered as follows: sinus tachycardia, sinus bradycardia, sinus arrhythmia, supraventricular ectopic beats, ventricular ectopic beats, atrial tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, nodal rhythm, the first, second and third degree of heart blocks, bundle branch block and so on.

The discussion about the incidence of these arrhythmias in hyperbaric oxygenation is the point of interest.

Cameron[25][26] described the incidence of serious arrhythmias in the investigation of 18 patients of the caisson group and 18 control patients. There were 3 cases of serious arrhythmia in the caisson group including two with complete heart block, both of whom died, and one with auricular fibrillation who survived. In the control group, there were 4 cases including one complete heart block, who died, one with auricular fibrillation, who died, and 2 with auricular fibrillation, who survived.

Elk[11][12] described that in all animals in the control group, multifocal ventricular ectopic beats and ventricular tachycardia occurred, and then, these arrhythmias developed to ventricular fibrillation. In 16 per cent of the caisson group, ventricular ectopic beats and ventricular tachycardia occurred, and followed by ventricular fibrillation.

In the present study, ventricular tachycardia and ventricular ectopic beats occurred in 60 per cent of the caisson group and in 46 per cent in the control group. In those animals of the caisson group, ventricular ectopic beats and ventricular tachycardia were frequently occurred in the chamber during hyperbaric condition. Only one animal with frequent ventricular ectopic beats in the caisson group survived for 30 days. However, the remainder with the arrhythmia in both groups died within 7 days after embolization.

As described by Harris[46], the cells in the boundary zone between ischemic and nonischemic area become hyperexcitable and give rise to discharges of electrical current, and then, the heart becomes irritable. The high irritablity of the heart may develop to ventricular ectopic beats or ventricular tachycardia, and further to ventricular fibrillation. If so, it would be considered to be acceptable that by hyperbaric oxygenation, the gradient of oxygen tension across the transitional zone may become more significant difference than at normal pressure in room air, and then, the heart may be irritated.

ST segment change by hyperbaric oxygenation was described by several authors. The diminution of ST deviation in hyperbaric oxygenation has been described by Roshe[8]. The marked elevation of the ST segment after infarc-

tion decreased within 1 mV for 20 minutes in 100 per cent of the animals of the caisson group, and following decompression to 1 ATA, the ST segment again elevated in all animals.

Petropoulos[10] described also that the marked alteration of the ST segment and the other ischemic changes by ligation of the left circumflex coronary artery became less or regressed to normal during the first 8 to 25 minutes at 3 ATA in oxygen, and after decompression these ischemic patterns gradually reappeared.

In the present experiment, there was an improvement of the ST segment change in hyperbaric oxygenation. However, the change was reversible, and after the decompression the deviation of the ST segment returned to the level before the treatment.

By hyperbaric oxygenation, especially at 3 ATA in oxygen, there was a tendency of regression of the ischemic pattern in ECG findings.

In the course of survival, the deviation of the ST segment decreased more rapidly in the caisson group than in the control group.

These results suggest that hyperbaric oxygenation is beneficial in the treatment of myocardial infarction.

SGOT and SGPT: Mathur[47] reported in his experimental studies that a rise in the serum transaminase activity was seen after ligation of the coronary artery. In all cases with demonstrable myocardial necrosis, the amount of serum enzymes showed a sharp rise in the specimen obtained at 6 hours, reaching to a peak in 18 to 28 hours (SGOT), and 18 to 24 hours (SGPT). The rise was followed by rapid decline initiated during the next 24 hours and a more gradual fall subsequently, returning to the near normal values in 4 to 6 days.

It was reported by several authors that the relation between hyperbaric oxygenation and the changes of SGOT and SGPT level after myocardial infarction were investigated experimentally or clinically.

Meijne[3,4] investigated the comparison between the caisson group and the control group after ligation of the left anterior descending artery and the average maximum value of SGOT was 277, and that in the control group was 526 units.

Harris[14] reported the changes of SGOT level under several conditions in dogs. In the group of animals anesthetized and intubated only, SGOT showed a variation from 16 to 41 units. In the group of animals with thoracotomy only and breathing room air, the average value was 64. In the group of animals without surgery and exposed to 100 per cent oxygen at 2.5 ATA, it was noted that no dog showed a significant elevation of SGOT.

In the group of animals with thoracotomy and ligation of the left anterior descending artery, breathing in room air, SGOT showed a rise at the end of

8 hours with an average rise to 126. In the last group of animals with thoracotomy and ligation of the left anterior descending artery, and exposed to 100 per cent oxygen at 2.5 ATA for 8 hours, SGOT showed a rise at the end of 8 hours with an average rise to 120.

In the present study, SGOT and SGPT in animals without embolization procedure and exposed to 100 per cent oxygen at 3 ATA were investigated. The value of SGOT or SGPT showed a rise at the end of 6 hours with an average rise to 59 or 33, and reached a peak at the end of 24 hours with an average rise to 76 or 42, and then, the value was followed by a decline to the near normal level at the end of 3 days. The maximum average value of SGOT and SGPT indicated higher in the caisson group than in the control group. However, SGOT and SGPT after the peak reduced more rapidly in the caisson group than in the control group.

Pathological findings: By the description of Broldi[48], coronary thrombosis in human being occurred in the highly sclerotic vessel, and with the exception of a few instances, all associated with a correspondingly well developed collateral circulation. It seems that the ischemic state produced by experimental coronary occlusion is not identical with myocardial infarction in human being.

Grayson[49] reported the pathological findings of myocardial infarction in dogs by acute ligation of the coronary artery. The heart within 15 minutes after occlusion showed no macroscopic changes, and in the dogs died 45 minutes after ligation there was already a clear macroscopic lesions of wide spread ischemia clearly distinguished from the surrounding tissue. After 4 hours, myocardial infarction was always well established.

Shnitaka[50] reported the histological alteration in dogs after ligation of the anterior descending artery. Between 3 and 6 hours after coronary artery ligation, the changes consisted of congestion of capillaries and small vessels, slight interstitial edema and the margination of a small number of neutrophils in congested vessels. In infarction of 12 hours' duration, morphologic changes of ischemic necrosis were also evident. Muscle fibers were hyalinized, dense, acidophilic and shrunken. Myofibrils showed partial loss of cross striation and fragmentation.

After 24 hours, the peripheral portions of infarction became heavily infiltrated with neutrophils. In myocardial infarction of 48 hours' duration there was increased interstitial edema, acidophilia of necrotic muscle fibers and extensive dissolution of myofibrils.

After 3 days, the leucocytic infiltration had spread centrally to involve the entire ischemic area, and some neutrophils showed degenerative changes. After 7 days, only the shadowy outlines of muscle structure were evident in the area of infarction. The remaining muscle components showed hyalinization and

acidophilia. At the periphery of large infarction and throughout much smaller patchy infarction, replacement of necrotic muscle with grannulation tissue containing proliferating fibroblasts developed. After 2.5 weeks there was partial replacement of necrotic muscle by maturing granulation tissue which extended inwards from the periphery.

In the description of Baroldi[48], histological changes in the course of myocardial infarction were classified as the following 5 stages: 1) Early coagulation necrosis stage, 2) Leucocytic infiltrative stage, 3) Early phase of organization, 4) Granulomatous stage, 5) Fibrosis stage.

Trapp[5,6] investigated the size of the infarcted area in dogs with the left anterior descending artery ligated. The results obtained was expressed as a percentage of the ischemic muscle to the entire heart. The percentage in the caisson group was 7.6 per cent, as compared with 11.89 per cent in the control group.

Petropoulos[10] investigated in dogs after ligation of the circumflex artery. Dogs of the caisson group had transmural infarction measuring about 3 cm in diameter on the average. Dogs of the control group presented transmural infarction measuring 4.2 cm in diameter on the average.

In the first stage experiment of the present study, among the animals which lived longer, some with the severe form of myocardial infarction noted pathologically were found. This was presumably related to the finding that hyperbaric oxygenation prolonged the life of the animal and permitted the pathological process of myocardial infarction to evolve histologically. The control animals, on the other hand, died apparently before actual infarction could be identified histologically. The results suggested that hyperbaric oxygenation may lengthen the life after myocardial infarction, and the prolongation of the life permits the development of pathologically detectable myocardial infarction.

However, by the second stage experiment, the gross appearance of 7 and 10 days survival in the caisson group revealed the findings of the development of the protective effect of hyperbaric oxygenation, and the difference of the histological findings between the caisson group and the control group demonstrated the detectable effect of hyperbaric oxygenation on the ischemic process after myocardial infarction.

Microangiography: The alteration of the blood supply to the region of myocardial infarction, especially in hyperbaric oxygenation, is not determined clearly. Present studies investigated these changes of revascularization of the small coronary arteries or capillaries in hyperbaric oxygenation by microangiographic studies.

In 1938, Schlesinger[51] stated that coronary arteries were true end arteries without intercommunication. However, as described by Bloor[52], Schlesinger's

view was later modified to the statement that interarterial anastomoses in a normal heart were not greater than 40 μ in diameter, if there was no associated disease affecting either the coronary arteries or the myocardium.

By Bloor's report, 4 types of collateral vessels in the heart can be distinguished: endomural, intercoronary, retrocardiac and tansepicardial.

Vineberg[53] considered these vessels to carry oxygenated blood to the ischemic myocardium, and to contribute to revascularization procedure.

These anastomoses have been investigated by means of a few various techniques.

By Robins[54] these comprised 1) macroscopic demonstration of a vessel bridging between two or more coronary arteries, 2) the findings of mass introduced into one coronary artery in the territory of another, and, 3) the appearance of mass distal to coronary obstruaction. These techniques are available to investigate myocardial revascularization after coronary occlusion.

Senderoff[55] reported the postmortem barium injection studies on the hearts of dogs removed at verious time intervals after ligation of the left anterior descending artery. In those dogs dying within the first 24 hours, there was a large bare area containing no barium corresponding to the area of distribution of the ligated coronary artery. In dogs surviving about 30 days, there were varying amounts of barium present in the anterior descending coronary artery. This barium was noted to enter in a retrograde fashion from several intercoronary anastomoses with adjacent vessels.

In the present studies, it was demonstrated that the further revascularization in the myocardium after myocardial infarction was developed in the group treated with hyperbaric oxygenation, as compared with the control group. These results seem to suggest that hyperbaric oxygenation is able to permit the maintenance of oxygen supply to the region following by the development of vessels by revascularization.

With abrupt cessation of flow through a coronary artery after myocardial infarction, hypoxia develops quickly. If each mass of heart muscle is supplied only from one artery through its terminal branch, it could not be expected that hyperbaric oxygenation is beneficial.

However, recognizing the richness of coronary collateral artery within the myocardium, it seems reasonable to expect to provide increased oxygen tension in the region by hyperbaric oxygenation.

The improvement in survival figures is strikingly similar to the thought obtained by Alttar[56] in the treatment of hemorrhagic shock.

According to his opinion, it was concluded that the improved tissue oxygenation provided by dissolved oxygen under high pressure is believed to provide cellular integrity during hemorrhagic shock.

CONCLUSION

When the results from the present study suggesting the protective effect of hyperbaric oxygenation on the ischemic process after myocardial infarction is considered, it is only logical to conclude as follows;

1) There may be an improvement of the collateral circulation during the treatment by hyperbaric oxygenation.

2) The same amount of blood available by the collaterals may carry a greater amount of oxygen by hyperbaric oxygenation.

3) More oxygen may be transported, notwithstanding that oxygen may cause vasoconstriction.

4) The diffusion of oxygen through tissue fluid or pericardial fluid may play an important role.

By these view points, it would be concluded that hyperbaric oxygenation exerts a beneficial effect on myocardial infarction.

SUMMARY

In the present experiment of 46 dogs, the coronary artery was embolized by injecting microspheres of 40 μ in diameter. In order to evaluate the influence of oxygen treatment at 3 ATA on myocardial infarction, the investigation on the mortality, hemodynamic changes, ECG findings, SGOT, SGPT, pathological findings of the infarcted lesion and microangiographic studies of the lesion were performed.

The results were analyzed and discussed, as follows;

1) The mortality in the early period after embolization was not reduced by hyperbaric oxygenation, and it seems to suggest that the treatment by hyperbaric oxygen did not protect ventricular fibrillation.

Survival rate in the late period revealed higher in the caisson group than in the control group.

2) Cardiac rate decreased moderately with hyperbaric oxygenation. Arterial pressure increased slightly under hyperbaric condition. However, these hemodynamic effects returned to the level before treatment when animals were removed from hyperbaric condition.

3) Ventricular tachycardia and ventricular ectopic beats occurred more frequently in the hyperbaric condition than in the control condition. It seems to suggest that cardiac irritability may be promoted by hyperbaric oxygenation.

4) The deviation of the ST segment decreased by hyperbaric oxygenation, and these changes were reversible. However, in the course of survival, the deviation of the ST segment was improved more rapidly in the caisson group than in the control group.

5) The maximum level of SGOT and SGPT did not differ detectably between in the caisson group and in the control group. SGOT and SGPT in the descending course after the peak were improved more rapidly in the caisson group than in the control group.

6) The extent of infarction was significantly less in the caisson group in the later period after embolization.

The histological findings at the margin of the lesion showed further regenerative improvement in the caisson group.

7) Microangiographic studies showed that revascularization was developed more progressively in the caisson group.

These results suggested the protective effect of hyperbaric oxygenation on the ischemic process after myocardial infarction.

In the present study, it would be concluded that hyperbaric oxygenation exerts a beneficial effect on myocardial infarction.

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REFERENCES

1) Smith, G. and Lawson, D. A., Experimental coronary artery occlusion: effects of the administration of oxygen under pessure, *Scot. Med. J.*, **3**, 346, 1958.
2) Illingworth, C. B. E., Treatment of arterial occulusion under oxygen at two atmospheres pressure, *Brit. Med. J.*, **17**, 5315, 1962.
3) Meijine, N. G., Bulterjs, A. B., Schoemaker, G. and Eioff, S. J. P., Treeatment of dogs with oxygen under high atmospheric pressure, after ligation of the descending branch of the left coronary artery, *Dis. Chest*, **44**, 234, 1963.
4) Meijne, N. G., Schoemaker, G. and Bluterijs, A. B., Oxygensupply to ischemic myocardial tissue under increased atmospheric pressure, Edited by Boerema, I., Brummelkamp, W. H. and Meijne. N. G., In.: Clinical application of hyperbaric oxygsnation, Elsevier Publishiug Company, Amsterdam, 1964, p. 69.
5) Trapp, W. G. and Creighton, R., Experimental studies of increased oxygen pressure on myocardial ischemia after coronary ligation, Edited by Boerema, I., Brummelkamp, W. H. and Meijne, N. G., In: Clnical application of hyperbaric oxygenation, Elsevier Publishing Company, Amstrdam, 1964, p. 101.
6) Trapp, W. G. and Creighton, R., Experimental studies of increased atmospheric pressure on myocardial ischemia after coronary ligation, *J. Thorac. Cardiv. Surg.*, **47**, 687, 1964.
7) Trapp, W. G., Hyperbaric oxygen and eardiac infarction, *Dis. Chest*, **47**, 367, 1965.
8) Roshe, J. and Allen, W., Effects of hyperbaric oxygenation on left circumflex coronary artery occlusion in dogs, *Surg. Forum*, **15**, 208, 1964.
9) Chardack, W. M., Gage, A. A., Federico, A. J., Cusick, J. K., Matsumoto, P. J. H. and

Lanphier, E. H., Reduction by hyperbaric oxygenation of the mortality from ventricular filbrillation following coronary artery ligation, *Circ. Res.*, **15**, 497, 1964.

10) Petropoulos, P. C. and Boerema, I., Influence of hyperbaric oxygenation on the hemodynamic changes and mortality after circumfiex coronary occlusion, Edited by Boerema, I., Brummelkamp, W. H. andMeijne, N. G., In: Clinical application of hyperbaric oxygenation, Elsevier Publishing Company, Amsterdam, 1964, p. 84.
11) Elk, J. V. and Trippel, O. H., Ventricular fibrillation following coronary occlusion in dog heart and the possible protective effect of high pressure oxygen, Edited by Boerema, I., Brummelkamp, W. H. and Meijne, N. G., In: Clinical application of hvperbaric oxygenation, Elsevier Publishing Company, Amsterdam, 1964, p. 116.
12) Elk, J. V. and Benvenuto, R., Prevention of ischemic ventricular fibrillation by high pressure oxygen in dog, Edited by Ledingham, I. M., In: Hyperbaric oxygenation, proceedings of the second international congress., The Darien Press LTD., Edinburgh, 1965, p. 307.
13) Hunter, S. W., Long, S. V., Berger, E. C. and Britton, D., Coronary occlusion, total and subtotal, under and hyperbaric condition, Edited by Boerema, I., Brummelkamp, W. H. and Meijne, N. G., In: Clinical application of hyperbaric oxygenation, Elsevier Publishing Company, Amsterdam, 1964, p. 105.
14) Harris, R. H. and Hitchcock, C. R., Serum transaminase levels (SGOT) in dogs with induced myocardial infarction treated with hyperbaric oxygenation, Edited by Boerema, I., Brummelkamp, W. H. and Meijne, N. G., In: Clinical application of hyperbaric oxygenation, Elsevire Publishing Company, Amsterdam, 1964, p. 110.
15) Edwards, W. S., Holdefer, W. F. and Dimick, A., Factors limiting survival after circulatory occlusion under hypotermia and hyperbaric oxygenation, *J. Thrac. Cardiv. Surg.*, **50**, 1965, 839.
16) Turnbull, A. D., Mac Lean, L. D., Dobell, A. R. and Demers, R., The influence of hyperbaric oxygen and of hypoxia on the ventricular fibrillation threshold, *J. Thorac. Cardiv. Surg.*, **50**, 1965, 842.
17) Gage, A. A., Federico, E. F., Lanphier, E. H. and Chardack, W. M., The effect of hyperbaric oxygenation on the mortality from ventricular fibrillation following coronary artery ligation, Edited by Ledingham, I. M., In: Hyperbaric oxygenation, proceedings of the second international congress., The Darien Press LTD., Edinburgh, 1965, p. 288.
18) Robertson, H. F., The effect of hyperbaric oxygenation on myocardial infarction in dogs, *Canae. J. Surg.*, **9**, 81, 1966.
19) Jacobson, J. H., Wang, M. C. H., Yamaki, T., Kline, H. J., Kark, A. E. and Kuhn, L. A., Hyperbaric oxygenation, Diffuse myocardial infarction, *Arch. Surg.*, **89**, 905, 1964.
20) Jacobson, J. H., Wang, M. C. H., Yamaki, T., Kline, H. J., Kark, A. K. and Kuhn, L. A., Hyperbaric oxygenation in diffuse myocardial infarction, Edited by Ledingham, I. M., Hyperbaric oxygenation, proceedings of the second international congress, The darien Press LTD., Edinburgh, 1965, p. 295.
21) Kuhn, L. A., Kline, H. J., Wang, M., Yamaki, T. and Jacobson, J. H., Hemodynamic effects of hyperbaric oxygenation in experimental acute myocardial infarction, *Circ. Res.*, **16**, 499, 1965.
22) Kuhn, L. A., Kline, H. J., Wang, M., Yamaki, T. and Jacobson, J. H., Hemodynamic effect of hyperbaric oxygenation in acute myocardial infarction, *Clin. Res.*, **12**, 187, 1964.
23) Holloway, D. H., Whalen, R. H., Saltzman, H. A., and Mcintosh, H. D., Hyperbaric oxygenation in the treatment of acute coronary artery embolization in dogs, *J. Lab. Clin. Med.*, **66**, 596, 1965.
24) Peter, H. R., Rau, R. W., Whalen, R. E., Entman, M. L. and Mcintosh, H. D., Effects of hyperbaric oxygenation on coronary artery occlution in pigs. *Circ. Res.*, **89**, 1966.

25) Cameron, A. J. V., Gibb, B. H., Ledingham, I. M.. McGuinness, J. B., Norman, J. N. and Sharif, M., A controlled clinical trial of hyperbaric oxygen in the treatment of acute myocardial infarction. Preliminary results, Edited by Boerema, I., Brummelkamp, W. H. and Meijne, N. G., In: Clinical application of hyperbaric oxygenation. Elisever Publishing Company, Amsterdam, 1964, p. 75.
26) Cameron, A. J. V., Gibb, B. H., Ledingham, I. M. and McGuinness, J. B., A controlled clinical trial of hyperbaric oxygenation in the treatment of acute myocardial infarction, Edited by Ledingham, I. M., In: Hyperbaric oxygenation, proceedings of the second international congress., The Darien Press LTD., Edinburgh, 1965, p. 277.
27) Cameron, A. J. V., Hutton, I., Kenmure, A. C. F. and Murdoch, W. R., Hemodynamic and metabolic effects of hyperbaric oxygenation in myocardial infarction, Lancet, 15, 833, 1966.
28) Saltman, H. A., Hyperbaric oxygenation in cardiovascular disease, *Circulation*, **31**, 454, 1965.
29) Moon, A. J., Williams, K. G. and Hophinson, W. I., A patient with coronary thrombosis treated with hyperbaric oxygen, **4**, 18, 1964.
30) Nielsen, B. L. and Marner, I. L., Shock in acute myocardial infarction, *Acta. Med. Scand.*, **175**, 65, 1964.
31) Hurwitz, M. and Eliot, R. S., Arrhythmia in acute myocardial infarction, *Dis. Chest*, **45**, 671, 1964.
32) Day, H. W. and Averill, K., Recorded arrhythmias in acute coronary care area., *Dis. Chest.*, **49**, 133, 1966.
33) Julian, D. G., Valentine, P. A. and Miller, G. G., Disturbances of rate, rhythm and conduction in acute myocardial infarction, *Amer, J. Med.*, **37**, 915, 1964.
34) Pifarre, R. and Hufagel, C. A., An experimental study comparing the acute occlusion of the anterior descending and the left circumflex coronary arteries, *J. Thorac. Cardiv. Surg.*, **51**, 761, 1966.
35) Chardack, W. M., Bolgan, F. J., Olson, K. C., Gage, A. A. and Fransmorth, W. E., The mertality following ligation of the anterior descending branch of the left coronary artery in dogs, *Ann, Surg.*, **141**, 443, 1955.
36) Lumb, G. and Singletary, H. P., Blood supply to atrioventricular node and bundle of his: a comparative study in pig, dog and man., *Amer. J. Path.*, **41**, 65, 1962.
37) Coffman, J. D. and Gregg, D. E., Oxygen metabolism and oxygen dept repayment atter myocardial ischemia, *Amer. J. Physiol.*, **201**, 881, 1961.
38) Kuhn, L. A., Gruber, F. L., Frankel, A. and Kupfer, S., Hemodynamic effects of extracorporeal circulation, *Circ. Res.*, **8**, 199, 1960.
39) Kuhn, L. A., Apter, R., Weinrauch, H., Jacobson, T. E. and Meltzer, L., Hemodynamic and metabolic effects of skin and blood stream cooling in experimental myocardial infarction with shock, *Amer. J. Cardiol.* 795, 1963.
40) Green, H. D. and Wegria, R., Effects of asphyxia, anoxia and myocardial ischemia on coronary blood flow., *Amer. J. Physiol.*, **135**, 271, 1942.
41) Eckcnhoff, J. E., Hafkenschiel, J. H. and Landmessser, C. M., Coronary circulation in dog., *Amer. J. Physiol.*, **148**, 582, 1947.
42) Hahnloser, P. H., Domanig, E., Lamphier, E. and Schenk, W. G., Hyperbaric oxygenation: Alterations of cardiac output and regional blood flow., *J. Thorac. Cardiov. Surg.*, **52**, 223, 1966.
43) MacLean, L. D. and Phibbs, C. M., Relative effect of chronic ischemia and a myocardial revascularization procedure on the ventricular fibrillation threshold., *Circ. Res.*, **8**, 473, 1960.
44) Spann, J. F., Moellering, R. C., Haber, E. and Wheeler, E. O., Arrhythmias in acute myocardial infarction, *New. Eng. J. Med.*, **271**, 427, 1964.

45) Kurland, G. S. and Pressman, D., The incidence of arrhythymias in acute myocardial infarction studied with a constant monitoring system, *Circulation*, **31**, 834, 1965.
46) Harris, A. S., Delayed development of ventricular ectopic rhythms following experimental coronary occlusion., Circulation, 1, 1318, 1959.
47) Mathur, K. S. and Sapru, R. P., Studies on the serum glutamic oxalacetic and serum glutamic pyruvic transaminases, and cardiac muscle transaminases in experimental myocardial infarction in dogs, *Ind. J. Med. Res.*, **51**, 36, 1963.
48) Baroldi, G., Acute coronary occulsion as myocardial infarction and sudden coronary heart death, *Am. J. Cardiol.*, **16**, 859, 1965.
49) Grayson, J. and Lapin, B. A., Observations on the mechanisma of infarction in dog after experimental occlusion of the corouary artery, *Lancet*, **11**, 1284, 1966.
50) Shnltaka, T. K., Nachlas, M. M., Histochemical alteraations in ischemic heart muscle and early myocardial infarction, *Amer. J. Path.*, **17**, 507, 1963.
51) Schlesinger, M. J., An injection plus dissection study of coronary artery occlusion and anastomoses, *Amer. Heart J.* **15**, 528, 1938.
52) Bloor, C. M. and Liebow, A. A., Coronary collateral circulation, *Amer. J. Cardiol.*, **16**, 238, 1965.
53) Vineberg, A., Deliyannis, T. and Pablo, G., The Ivalon sponge procedure for myocardial revascularization, *Surgery*, **47**, 268, 1960.
54) Robbins, S. L., Solomon, M. and Bennett, A., Demonstration of intercoronary anastomoses in human hearts with a low viscosity perfusion mass, *Circulation*, **33**, 733, 1966.
55) Senderoff, E., Welberry, A. E., Kaneko, M. and Baronofsky, I. D., Experience with attempts at ventricular defibriiation in the presence of acute coronary occlusion, Ann. Surg., **151**, 193, 1960.
56) Attar, S., Esmond, W. G. and Cowley, R. A. A., Hyperbaric oxygenation in vascular collapse, *J. Thorac. Cardov. Surg*, **44**, 759, 1962.