Cardiac Disturbances due to CO Poisoning in Experimental Animals

II. Changes of the Heart Excitability due to Acute CO Poisoning

By

Kenkichi Takahashi

*Department of Forensic Medicine, Tohoku University, School of Medicine,
Sendai; Director: Prof. Dr. T. Murakami*

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Changes of the heart in CO poisoning have been studied physiologically or electrocardiologically by many authors. But no report has been published concerning the excitability of heart as studied by the author in the present experiments. He presents some findings on the heart excitability utilizing electronic devices similar to those described in a fine monograph "Excitability of the heart" by Brooks and his collaborators¹⁾. Changes of the heart excitability are serious not only during CO gas inhalation, but also even after its cessation in experimental animals.

MATERIAL and METHOD

All experiments were performed upon mongrel dogs following the Brooks' technique. The animals were anesthetized with pentobarbital sodium of 30 to 40 mg per kg by intraperitoneal injection with supplement of this agent to prevent the spontaneous respiratory movement. While using artificial respiration of pure oxygen under positive pressure by the to and fro apparatus through the canister filled with soda-lime, the pericardium was opened lengthway following the incision to the left fifth intercostal space. Electrodes for driving were firmly attached to the epicardium of right auricular appendage with No. 1 silk threads. After the pacemaker was crushed, the heart was driven at a desirable rate (400 msec. interval, mainly) by thyatron discharge, the strength of which was adjusted to the level approximately twice the threshold. Both stimulating electrodes for testing and recording electrodes embeded in plastique were attached crosswise on the left ventricle in the same manner as driving electrodes. The test stimulus employed was a square wave pulse of which duration was 4 msec. and its amplitude could be varied. With some interval from R wave which was evoked by a driving electric pulse, the strength of a test stimulus was gradually in-

creased until an extrasystole was produced. The stimulus intensity at this moment was read on the oscilloscope screen by a current measurement device. With these procedures, the strength-interval curves in the cases of both normal condition and acute CO poisoning were plotted. Animals were poisoned with CO by the following procedure. CO gas freshly made was mixed with pure oxygen at the rate of 0.05, 0.25, 0.5 or 1% in the bag, which was connected to the canister. Animals inhaled this gas through the canister filled with soda-lime.

CO-hemoglobin (Hb) level was determined by Wolff-Schwerd method from the blood, which was drawn from a femoral artery at intervals of 15 minutes.

Blood pressure was recorded on a kymograph from the femoral artery by a mercury manometer.

RESULT

The experiments were performed upon twelve dogs. The CO concentration in the mixed gas used in the inhalation for 60 minutes was 0.05 to 1%. The 2.5% CO mixed gas was used in the inhalation for 15 minutes.

TABLE I. Duration of the Gas Inhalation and CO %
in the Gas

Animal No.	CO % in the mixed gas	Duration of the gas inhalation
109, 119	0.05	60 minutes
101, 104	0.25	" "
55, 57, 60	0.5	" "
79, 82, 92	1.0	" "
106, 132	2.5	15 "
86, 96, 99	Control	

The results are shown in Table II.

The change of the strength-interval curve: In control animals, the absolute refractory periods (A.R.P.) and the relative refractory periods (R.R.P.) were both prolonged as time went by. After about 60 minutes, No. 85 (Fig. 1) and No. 99 showed 5 msec. prolongation in A.R.P. and 15 msec. prolongation in R.R.P., and No. 96 showed a few msec. prolongation in A.R.P. The change of resting threshold was not observed. After about 120 minutes, in all control animals, the refractory periods were prolonged still more, but there was no change in resting thresholds. Thus the strength-interval curves in control animals shifted to the right side and the bounds of those shifts were within 5 msec. after 60 minutes,

TABLE II. Changes of Heart Excitability

Animal No.	CO %	Duration of inhal.*	Time of determination**	A.R.P. (m sec.)	R.R.P. (m sec.)	Resting threshold (mA)	Site of dip	Prol. A.R.P. (mA)	Prol. R.R.P. (mA)	Blood pressure (mmHg)
109	0.05	60	before	132	190	0.15	145			50- 60
			20- 45	143	210	0.15	170	11	20	45- 55
			60- 80	152	225	0.15	180	20	35	40- 45
			120-145	155	230	0.15	185	23	40	40
119	0.05	60	before	130	200	0.14	146			70- 75
			15- 29	135	300	0.14	150	5	0	60- 75
			60- 77	150	210	0.14	170	20	10	60- 65
			105-122	150	220	0.14	175	20	20	60
101	0.25	60	before	140	195	0.30	165			70- 75
			20- 58	145	210	0.30	175	5	15	90
			95-125	148	230	0.35	180	8	35	80- 90
104	0.25	60	before	130	205	0.25	160			80- 85
			19- 41	145	205	0.25	170	15	0	70- 80
			55- 74	150	220	0.25	170	20	15	85- 95
			120-148	160	235	0.25	185	30	30	80- 90
55	0.5	60	before	185	260	0.2	200			80-100
			40- 60	200	270	0.2	210	15	10	90-105
			110-140	200	270	0.25	210	15	10	80- 90
57	0.5	60	before	140	220	0.25	155			90- 80
			10- 50	140	210	0.3	160	0	-10	100- 85
			25-110	150	210	0.3	170	10	-10	70- 80
60	0.5	60	before	160	260	0.25	185			75- 60
			30- 50	175	260	0.25		15	0	70- 85
			65- 88	180	280	0.25		20	20	70- 80
			100-120	185	280	0.25		25	20	70
79	1.0	60	before	165	260	0.3	185			90-105
			55- 77	170	260	0.3	190	5	0	85-100
			103-127	175	260	0.4	200	10	0	70
			145-170	175	260	0.4	200	10	0	75
82	1.0	60	before	160	240	0.25	175			55- 60
			15- 41	170	240	0.25	180	10	0	60- 70
			108-135	170	230	0.3	185	10	-10	60- 70
			163-188	170	230	0.3	180	10	-10	60- 45
92	1.0	60	before	145	195	0.2	155			85- 90
			18- 37	150	195	0.2	160	5	0	80- 90
			50- 70	170	215	0.2	175	25	20	70- 80
			135-160	180	230	0.2	180	35	35	80- 85
122	2.5	15	before	110	175	0.12	115			55- 60
			2- 22	105	175	0.12	115	0	0	50- 70
			50- 73	110	180	0.12	120	5	5	60- 70
			120-148	110	180	0.12	125	5	5	55- 75
			180-213	110	180	0.12	120	5	5	60- 80
106	2.5	15	before	125	190	0.11	140			110-120
			2- 11	115	200	0.11	135	0	10	120
			60- 84	120	200	0.11	135	0	10	110-115
			120-138	120	200	0.11	140	0	10	90-100

* minutes

** minutes after the start of gas inhalation

TABLE II. (Continued.)

Animal No.	CO %	Duration of inhal.*	Time of determination**	A.R.P. (m sec.)	R.R.P. (m sec.)	Resting threshold (mA)	Site of dip	Prol. A.R.P. (mA)	Prol. R.R.P. (mA)	Blood pressure (mmHg)
86	Control		0-30	115	195	0.1	135			85-95
			60-87	120	195	0.1	135	5	0	80-85
			120-165	120	205	0.1	140	5	10	70-80
			180-215	125	205	0.1	145	10	10	80-90
96	Control		0-20	150	230	0.13	175			110-90
			50-70	153	225	0.13	175	5	-5	70-90
			100-135	160	220	0.13	185	10	-10	70-90
99	Control		0-25	130	210	0.14	155			75-90
			50-75	135	210	0.14	160	5	0	80-90
			110-148	135	215	0.14	160	5	5	85-100

Fig. 1. Change of the heart excitability in control animal as time goes by.

5 to 10 msec. after 120 minutes and 10 msec. after 180 minutes. And the level of resting threshold was kept horizontally.

Due to the inhalation of 0.05% CO gas for 60 minutes, the remarkable prolongation of refractory periods was observed. In two animals (Nos. 109 and

119), the prolongation of A.R.P. was 5 to 10 msec. during the gas inhalation, and 18 msec. after the gas inhalation. The prolongation of R.R.P. was also remarkable in both animals and reached to 35 msec. in No. 109 (Fig. 2). The site of dip shifted to the right and the level of dip decreased remarkably in No. 119. The level of resting threshold was not varied in both animals. Thus the shift of strength-interval curves was remarkable and continued after the cessation of gas inhalation. The degree of shifts was remarkable until 60 minutes after the cessation of gas inhalation, and was at leisure afterwards.

Fig. 2. Change of the heart excitability in No. 109 animal poisoned with 0.05 % CO gas inhalation for 60 min.

The shifts due to the inhalation of 0.25% CO gas for 60 minutes were almost similar to those described above. In No. 104 (Fig. 3), the shift was remarkable and the bound was 15 msec. during the gas inhalation and was 30 msec. after the cessation of gas inhalation. In No. 101, the degree of shift was not remarkable and the bound was within 5 msec. during the gas inhalation and 8 msec. after the cessation of gas inhalation. The level of resting thresholds did not change in No. 104 and was raised by about 0.05 mA in No. 101.

Due to the inhalation of 0.5% CO gas for 60 minutes, the strength-interval curves shifted to the right side similarly. These shifts continued after the cessation of gas inhalation. The prolongation of A.R.P. was 10 to 25 msec. and

Fig. 3. Change of the heart excitability in No. 104 animal poisoned with 0.25% CO gas inhalation for 60 min.

Fig. 4. Change of the heart excitability in No. 92 animal poisoned with 1 % CO gas inhalation for 60 min.

those of R.R.P. were 10 to 20. msec. In two animals (Nos. 55 and 57) out of three, the elevation of resting threshold was observed and in No. 60, the dip which was observed before the gas inhalation disappeared during and after the gas inhalation.

Due to the inhalation of 1% CO gas for 60 minutes, the strength-interval curves showed similar shifts. In No. 92 (Fig. 4), the prolongation of A.R.P. reached 45 msec. The level of resting thresholds did not change in two animals out of three and was elevated in the other animal.

Due to the inhalation of 2.5 % CO gas for 15 minutes, the prolongations of A.R.P. were 5 msec. and those of R.R.P. were 5 to 10 msec. The level of resting threshold did not change. The shift of strength-interval curves in this group was slight and the bound of shift was within the control.

CO-Hb level (Fig. 5): The CO-Hb concentration was determined every 15 minutes. The CO-Hb levels were increasing quickly for 15 to 30 minutes after the start of gas inhalation and slowly afterwards. In 60 or 120 minutes

Fig. 5. CO-Hb concentration in blood during and after the CO gas inhalation.

after the cessation of gas inhalation, the levels were nearly the same as before the gas inhalation. The progress of CO-Hb levels was almost similar to one another in animals poisoned with CO gas inhalation in spite of the difference of CO concentration in mixed gas, which was inhaled.

Blood pressure: The blood pressure was observed as a guide of experiments. The blood pressure was lowered to some degree by anesthetic and chirurgic procedures. The elevation and drop of blood pressure during and after the gas inhalation were within 10 to 20 mm Hg except No. 79 in which the blood pressure change reached 30 mm Hg.

DISCUSSION

In control animals, the shift of strength-interval curve to the right is observed and the prolongation of A.R.P. is within 5 msec. In the experiments with the inhalation of 0.05 to 1% CO gas for 60 minutes, all animals show the prolongation of refractory periods and the strength-interval curves are shifted to the right remarkably. The degree of shifts in poisoned animals is nearly or over twice as much as those in control animals. The resting threshold is not varied in control animals and the majority of poisoned animals, but is elevated in a few poisoned animals. Then it is conceivable that the excitability of the heart muscles is decreased in the acutely poisoned animals with the inhalation of CO gas, and this decrease takes place during the gas inhalation and continues after the cessation of gas inhalation, the decrease being remarkable for a certain time after the cessation of CO gas inhalation. Results similar to those shown in my experiments were observed in the cooled heart as well as in the anoxic heart. Haugnauer and Covino²⁾ observed the shift to the right in the strength-interval curve by cooling experiment, and on the other hand, Brooks *et al.*³⁾ described the prolongation of refractory period and the elevation of resting threshold at low temperature. The present study shows the result similar to those of the cooling experiment and the findings in the anoxic stage of the heart obtained by Yanagita⁴⁾ and Murotsu⁵⁾ in our laboratory.

The CO-Hb levels showed increases, which reached nearly 20% in animals poisoned with the inhalation of 0.05% CO gas for 60 minutes and over 40% in those poisoned with the inhalation of 0.5 to 1% CO gas for the same duration. The concentration of O₂-Hb in blood decreases because of the increase of CO-Hb and it is clear that the amount of oxygen supplied to the heart muscles falls off. This principle is the same with hypoxia in anemia or in circumstance of hypo-oxygen. And in cooled hearts there is no lack of oxygen, but heart muscles cannot obtain enough oxygen from blood because of decreased dissociation of oxygen from Hb. It is certain that the abnormal findings under these conditions are attributed to the lack of oxygen in heart muscles. Therefore, the lowering of heart excitability in CO poisoned animals may be originated from anoxia

directly.

For a certain time after the cessation of CO gas inhalation, the animals showed the lowering of heart excitability, which became more remarkable. It may be attributed to disturbances of myoglobin and/or cytochrome c. Enzymatic activities of myoglobin and cytochrome c are due to Fe as well as hemoglobin. This Fe⁺⁺ combines with CO firmly and transformation from Fe⁺⁺ to Fe⁺⁺⁺ is checked. In CO poisoning, not only hemoglobin but myoglobin and/or cytochrome c combine with CO and after the cessation of CO gas inhalation, CO combined with hemoglobin is removed externally but yet CO combined with myoglobin and/or cytochrome c, remained in heart muscles, because of hard dissociation. Therefore, hypoxia of heart muscles continues after the cessation of CO gas inhalation, and this mechanism is responsible for the lowering of heart excitability, which continues and grows severe even after the cessation of gas inhalation.

Due to the inhalation of 2.5% CO gas for 15 minutes, animals showed little changes, which were within those observed in control animals. It may be due to the CO-Hb level, which is not so high as in the animals poisoned with the inhalation of CO gas for 60 minutes, and the time duration of gas inhalation is a main factor. In the animals poisoned with the inhalation for 60 minutes, the CO-Hb level was more than 40%, but in those for 15 minutes, it was less than 35%. It may require a certain time to make the heart less excitable. The level of CO-Hb may indicate the degree of CO inhalation but does not show the degree of CO poisoning in heart muscles, because there are differences between the affinities of CO to hemoglobin and myoglobin and/or cytochrome c.

It may be concluded that it requires a definite time duration for which the CO-Hb is maintained at a certainly high level, to produce the lowering of the heart excitability.

In the experiment with the inhalation of 2.5% CO gas for 15 minutes, the reduction of A.R.P. was observed. The same results were shown by Murotsu⁴⁾ in anemia and Yanagita⁵⁾ in low oxygen circumstances. They attributed the reason to the compensatory function in early stage of hypoxemia. The reduction in my experiments may be caused by the same mechanism.

The blood pressure was recorded as a guide for good progress of the experiment. The results described in this paper are limited to the date which did not show remarkable drop. And the elevation over 30 mm Hg was not observed during the CO gas inhalation.

SUMMARY

Changes of the heart excitability were observed in dogs poisoned acutely with the inhalation of CO gas.

1) Due to the inhalation of 0.05 to 1% CO gas for 60 minutes, the remarkable prolongation of refractory periods was observed in all animals and the

elevation of resting threshold was seen in a few animals. The lowering of heart excitability was shown not only during the gas inhalation but after its cessation. Then the strength-interval curve shifted to the right.

2) Due to the inhalation of 2.5% CO gas for 15 minutes, the heart excitability was decreased slightly during the gas inhalation and recovered soon by the inhalation of pure oxygen. Then the absolute refractory period was reduced.

It requires a definite time duration for which the CO-Hb level is maintained at a certainly high level, to produce the lowering of the heart excitability.

3) Lowering of the heart excitability continued and became severe after the cessation of gas inhalation. The disturbances of heart muscles due to CO poisoning may be attributed to disturbances of myoglobin and/or cytochrome c.

4) The reduction of absolute refractory period was observed by the inhalation of 2.5% CO gas for 15 minutes and this may be attributed to the compensatory function in the early stage of hypoxemia.

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