Effects of Carbon Monoxide Inhalation on Myocardial Infarct Size Following Experimental Coronary Artery Ligation

Souichiro SEKIYA, M.D.,* Sadayuki SATO, M.D.,*
Hiroshi YAMAGUCHI, M.D.,** and Kenichi HARUMI, M.D.***

SUMMARY

This study was conducted to determine whether or not a low concentration of carboxyhemoglobin influences the extent and severity of myocardial ischemia caused by coronary ligation. In 10 dogs, electrograms were recorded from 6 epicardial electrodes mounted on the anterior surface of the left ventricle and distributed over the area normally perfused by the lighted branch of the left anterior descending coronary artery. The magnitude of ST segment elevation of the 6 sites in each animal was determined for 15 min after ligation. This elevation was used as an index of the presence and severity of myocardial ischemic injury. Ligation alone increased Σ ST elevation, summed from 6 sites, from 2.06 ± 0.34 mV (SEM) to 24.89 ± 2.14 mV (SEM). Carbon monoxide inhaled prior to ligation increased the severity and extent of ischemic injury and the magnitude of ST segment elevation in the area peripheral to the ischemic area more than did ligation alone. These changes occurred without elevation of heart rate or arterial pressure. It was concluded that a low background concentration of carboxyhemoglobin at the time of ligation increased the extent and severity of myocardial ischemic injury.

Additional Indexing Words:

Epicardial electrography	ST segment elevation	Σ ST,
Myocardial ischemic injury	Hypoxia	Myoglobin

CARBON monoxide (CO) inhalation produces hypoxia as a result of an increase of carboxyhemoglobin (CO-Hb). It is harmful for those tissues with high oxygen demand such as the myocardium. There were some reports of the electrocardiographic changes due to CO poisoning. Takahashi¹⁾ re-

From the Departments of Physiology,* Public Health,** School of Medicine, Showa University, Tokyo and Division of Cardiology,*** Showa University, Fujigaoka Hospital, Yokohama.

Present address for reprint: Souichiro Sekiya, M.D., Division of Cardiology, Showa University, Fujigaoka Hospital, 1-30 Fujigaoka, Midori-ku, Yokohama 227, Japan.

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ported that gross electrocardiographic changes were rarely observed until the blood level of CO-Hb reached 40%. However, there was no evidence that a small concentration of CO-Hb in the blood would not affect electrocardiographic findings. CO is generated by incomplete combustion which occurs in automobile exhaust, in industrial effluent, in household heating, and in cigarette smoke. Habitual smoking is one of the coronary risk factors. The Framingham and Albany studies²⁾⁻⁴⁾ concluded that the mortality rate related to myocardial infarction and coronary heart disease of the heavy cigarette smoker was 3 times that of the nonsmoker. Recent smokers had higher peak creatine phosphokinase levels than either former smokers or nonsmokers, and it appears that infarctions are larger in recent smokers.⁵⁾

Ischemic ST segment depression occurred in 3 of 10 patients with classical exertional angina pectoris while breathing freeway air.⁶⁾ Becker et al⁷⁾ suggested from their animal experiment that low levels of CO-Hb may be harmful to patients with acute myocardial infarction. Goldsmith and Landaw⁸⁾ reported a relation between atmospheric CO and the fatality rates from myocardial infarction in Los Angeles. Although CO-Hb blood level may be 0.4–0.8% for nonsmokers it rises to about 10–15% for heavy smokers (more than 30 cigarettes/day).^{2), 3), 9)} The question may be posed as to whether the severity and size of myocardial infarctions are increased when the CO-Hb blood level seen in a heavy smoker is maintained.

We have studied the effects of a low concentration of CO-Hb on the electrocardiographic changes following experimental coronary ligation in dogs.

METHODS

Experiments were carried out on 10 dogs (10–15 Kg) anesthetized with sodium pentobarbital (35 mg/Kg, iv). Respiration was maintained with a Harvard respirator. The heart was exposed through a midsternal incision and suspended in a pericardial cradle. A branch of the left anterior descending coronary artery (LAD) was intermittently ligated with two silk-warmgut ligatures. Arterial pressure in the femoral artery was monitored with a Statham transducer.

Six sites on the anterior surface of the left ventricle were selected for epicardial electrogram (EG), one peripheral to the ischemic area and the others on the ischemic area from the center to the periphery (Fig. 1). A standard lead II electrocardiogram (ECG) was recorded, and the epicardial electrograms were taken with unipolar silver electrodes 1 mm in diameter mounted in plastic disks sutured to the epicardium. ECG and EG were monitored simultaneously with a cathode ray oscilloscope.

Fig. 1. Left panel: Schematic representation of the anterior surface of the heart in a dog, the left anterior descending coronary artery (LAD) and its branches, and sites of epicardial electrode placement (1 through 6). LA = left atrial appendage. The shaded area represents the area of injury after 15 min of ligation. Right panel: epicardial electrograms from sites 1 through 6 after 15 min of ligation under room air respiration.

Inspired gas was furnished from 2 bags (one filled with a 3,000 ppm CO and air mixture, the other with a 130 ppm CO and air mixture connected to the respirator input. The expired gas was not returned to the bags. A CO-Hb blood level concentration range of 13–15% was maintained by administering air with 3,000 ppm CO for the first 15 min, and then air containing 130 ppm CO for 1 hr. The CO in the expired air was measured by controlled potential electrolysis (CO tester EC-231: Riken Keiki Co) every 15 min and CO-Hb concentration in the blood was estimated by the following equation: $\text{CO-Hb (\%)} = 0.085 + 0.172 \times \text{CO in expired air (ppm)}$.¹⁰⁾

The coronary artery was ligated 3 times in each of 10 dogs. The first ligation was maintained for 15 min with room air respiration, and then released. One hour following the release of the first ligation CO inhalation was begun and 15 min after the start of CO inhalation, the second ligation was performed and maintained for 15 min and then released under CO inhalation. The third 15 min ligation was begun at the time that the CO-Hb blood level indicated 0% as determined by above equation with room air respiration.

Epicardial electrograms were obtained from the same sites throughout the experiments and were recorded before ligation and 1, 3, 5, 10, and 15 min after ligation without and with CO inhalation. The CO-Hb concentration in the blood was obtained before CO inhalation and at 15, 30, 45, and 60 min

Fig. 2. Electrocardiogram (lead II) and three epicardial electrograms before (control), 15 min, and 30 min after CO inhalation. No significant differences appear.

during the CO inhalation.

Data were analysed in the following way. Epicardial ST segment elevation at each site was measured in millivolts (1 mV=1 mm ST segment elevation). ST segment elevation exceeding 2 mV was considered abnormal, showing myocardial ischemic injury. In each animal, the values of the ST segment elevation from the 6 recording sites were added (Σ ST). This was used as the overall index to determine the severity of myocardial ischemic injury.^{11),12)} Σ ST 15 min after the ligation under room air respiration were used as controls. Σ ST of the controls were compared to Σ ST obtained at 15 min after the ligation under CO inhalation.

RESULTS

In almost all experiments no significant electrocardiographic changes were observed during the inhalation of the CO concentration used in our study, compared with room air respiration. In some cases, the heart rate was slightly increased for a few minutes after the start of CO inhalation. In the absence of coronary ligation, the inhalation of CO which raised CO-Hb blood levels to 14–15%, did not have any influence on ECG and ventricular EGs (Fig. 2).

After a coronary artery was ligated, the area supplied by the ligated artery became cyanotic and bulged during systole in almost all experiments. Tracings made after 15 min of the initial ligation of a branch of LAD under room air respiration are shown in Fig. 3A. EG-1, which was outside of the ischemic area, showed no change in ST segment, while recordings from EG-2 through EG-6, which were located inside the area of perfusion of the ligated artery, showed various degrees of ST segment elevation.

Fig. 4 illustrates the results from the same dog as in Fig. 3. Σ ST after 15 min of the first ligation increased from a control value of 3.3 mV to

Fig. 3. Six epicardial electrograms recorded in 1 subject after 15 min of ligation. (A): first ligation under room air respiration. (B): second ligation under CO inhalation.

Fig. 4. Σ ST elevation in 1 subject during first ligation under room air respiration (A), during second ligation under CO inhalation (B), and during third ligation under room air respiration (C).

22.6 mV.

After release of the ligation, the ST segment returned to the isoelectric line and Σ ST returned to the control value within 30 min (Fig. 5).

One hour after the release of the first ligation, CO inhalation was started. After a stable CO-Hb blood level (after 15 min of CO inhalation) was obtained, the second coronary artery ligation was repeated while CO inhalation was continued. In each animal, the degree of ST segment elevation seen at the sites of severe myocardial ischemia increased more than that observed in

Fig. 5. Σ ST elevation recovery to normal in 1 subject after first ligation during room air respiration (A) and after second ligation during CO inhalation (B).

the first ligation under room air respiration (Fig. 3B). On EG-2 and EG-3, the differences in the magnitude of ST segment elevation between the first ligation with room air respiration and the second ligation with CO inhalation were not significant; from EG-4 to EG-6, however, the magnitude of ST segment elevation in the second ligation under CO inhalation significantly increased.

Σ ST in the second ligation as shown in Fig. 4 increased more rapidly than that observed in the first ligation under room air respiration and increased from a control value of 3.1 mV before ligation to 30.8 mV 15 min after the second ligation.

The sequence of the recovery of Σ ST is shown in Fig. 5. Σ ST returned to the control value after release of 15 min ligation in both cases whether under room air or CO inhalation, but in the case of CO inhalation the recovery time was increased compared with room air respiration, and this tendency was observed in all experiments.

The changes in Σ ST from the first ligation under room air respiration to the second ligation under CO inhalation is summarized for all 10 days in Fig. 6. Σ ST during the first ligation with room air respiration increased from a control value of 2.06 ± 0.34 mV (SEM) before ligation to 24.89 ± 2.14 mV (SEM) after 15 min of ligation, while Σ ST during the second ligation with CO inhalation increased from a control value of 2.03 ± 0.33 mV (SEM) to 29.72 ± 3.16 mV (SEM) after 15 min of ligation. CO inhalation significantly increased the Σ ST compared to room air respiration ($p < 0.01$).

Table I shows the degree of ST segment elevation in 6 recording sites after 15 min of ligation. The amplitudes of ST segment elevation increased

Fig. 6. Summary of the results (10 dogs). Comparison between Σ ST elevation following 15 min of ligation under room air respiration and that under CO inhalation. * $p < 0.01$: first ligation under room air respiration vs second ligation under CO inhalation.

Table I. ST Segment Elevation of 6 Recording Sites after 15 Min of the First Ligation under Room Air Respiration and 15 Min of the Second Ligation under CO Inhalation

	EG-1	EG-2	EG-3	EG-4	EG-5	EG-6
1st ligation	0.54 ± 0.52	7.98 ± 0.74	7.58 ± 0.82	4.66 ± 1.24	2.55 ± 0.43	1.58 ± 0.86
2nd ligation	0.53 ± 0.53	8.18 ± 0.80	7.88 ± 0.89	6.59 ± 0.63	4.07 ± 1.05	2.60 ± 1.14
p value*	NS	NS	NS	$p < 0.01$	$p < 0.01$	$p < 0.05$

Results are expressed mean $\pm$ SEM of 10 subjects.

* Represents statistical significance of difference (1st ligation vs 2nd ligation).

NS=not significance.

significantly during the second ligation with CO inhalation, as compared to the value recorded during the first ligation with room air respiration on EG-4 ($p < 0.01$), EG-5 ($p < 0.01$), and EG-6 ($p < 0.05$), but were not significantly different on EG-2 and EG-3.

In 7 dogs Σ ST elevation during the third ligation with room air respiration showed similar increases in Σ ST elevation as were seen during the first ligation (Fig. 4C), and increased from 1.97 ± 0.30 mV (SEM) before ligation to 25.28 ± 2.62 mV (SEM) after 15 min of ligation. These results suggest that inhalation of low concentrations of CO in this experimental condition did not appear to produce irreversible damage to the myocardium.

DISCUSSION

Cigarette smoking is one of the major risk factors contributing to coronary heart disease, and increases the risk of developing coronary heart disease in the presence of hypertension and hypercholesterolemia.³⁾ Additionally, it has been reported that severe aortic and coronary artery atherosclerosis was present in a higher percentage of heavy smokers compared to nonsmokers.¹³⁾ Folts and Bonebrake noted that cigarette smoking contributed to the development of an acute occlusive platelet thrombus in a stenotic coronary artery.¹⁴⁾ Meanwhile, nicotine and CO are absorbed in the blood of cigarette smokers. Nicotine may increase catecholamine release from the adrenergic axon terminal within the cardiovascular system,¹⁵⁾ enhancing myocardial oxygen demand. Since CO has a 245-fold greater affinity for hemoglobin in comparison with that of oxygen, myocardial oxygen availability might be reduced in heavy smokers. Other authors reported that either nicotine or CO increased thrombotic tendency,^{16),17)} and reduced the ventricular fibrillation threshold during myocardial ischemia.^{18)–20)}

There are several reports^{21)–24)} on the morphological changes in the cardiovascular system caused by light chronic carbon monoxide exposure, but only a few reports on the electrocardiographic changes and the CO-Hb blood level. Acute carbon monoxide poisoning in humans or animals leads to electrocardiographic abnormalities and the development of arrhythmias. No objective signs were noted in dogs which were exposed to CO for 14 weeks, with a CO-Hb blood level of 14%.²⁵⁾ There was evidence of impending cardiac depression beginning at blood levels of 20% CO-Hb.²⁶⁾ As seen in the canine studies, with sudden elevation of CO-Hb concentration to 25%, coronary blood flow almost doubled without significant increases in cardiac output, femoral arterial pressure and heart rate, and the canine myocardium became hypoxic and showed evidence of anerobic metabolism when CO-Hb levels were acutely raised to 20–30%.²⁷⁾ Our study suggested that myocardial function would be maintained in a normal state at CO-Hb concentration level ranging from 13–15%. This concentration of CO-Hb had little influence on the balance between myocardial oxygen supply and demand in the normal state because there were no changes in heart rate, or femoral artery pressure, and the epicardial electrogram did not show any ST segment abnormality. But when the coronary artery ligation was performed during CO inhalation, the area of ischemic injury and the magnitude of ST segment elevation were increased compared with that without CO inhalation. The present study may suggest that a low concentration of CO-Hb may increase the extent of myocardial ischemic injury. Inhalation of CO deprives the oxygen trans-

port function to the myocardium not only of hemoglobin but also of myoglobin. Myoglobin has a higher affinity for CO than does hemoglobin, and myoglobin is saturated with CO concentrations approximately 2 or 3 times higher than the CO-Hb concentration seen at relatively low CO-Hb levels.²⁴⁾ Because of the displacement to the left of the oxygen dissociation curve of hemoglobin and myoglobin, the myocardial oxygen tension was decreased. The peripheral part of the ischemic area received oxygen from the ligated artery and the collateral artery. The latter is responsible for the progressive diminution of the size of the ischemic area seen in the case without CO inhalation, but this collateral circulation did not increase at the same rate during CO because of the effects of CO-Hb on blood flow. This was further verified by Sayen et al^{28), 29)} who noted a close correlation between the area of ST segment elevation and the reduction of myocardial oxygen tension. The evidence for this is based on Fig. 5 which shows that after release of ligation the time to recover to the normal state in the case under CO inhalation was much longer than that without CO inhalation.

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