EFFECTS OF SHORT-TERM EXPOSURE TO CARBON MONOXIDE IN PATIENTS WITH CORONARY ARTERY DISEASE

FINAL REPORT - EXECUTIVE SUMMARY

TO

CALIFORNIA AIR RESOURCES BOARD

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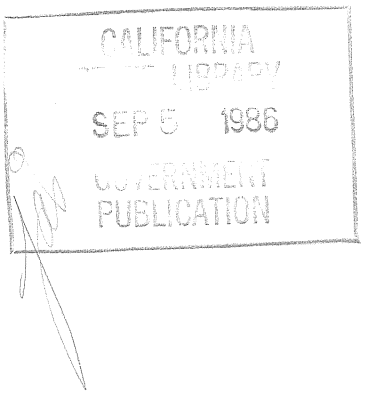

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The goal of this study was to examine the hypothesis that exposure to low levels of carbon monoxide (CO) would reduce the ability of persons with angina pectoris to perform exercise. Previous studies had indicated that CO exposures, sufficient to raise blood carboxyhemoglobin levels to about 3% of saturation, would result in a significant reduction in the length of time a subject with angina could exercize before the onset of typical symptoms of ischemia (*ie.* chest pain and/or changes in electrocardiogram patterns). Other studies, of persons with good health and normal cardiovascular and pulmonary function, showed that an objective measure of exercise tolerance, maximal O_2 uptake, was also adversely affected after low-level CO exposure. We therefore designed this study to examine both subjective and objective measures of exercise tolerance in subjects with stable angina pectoris, a disease in which chest pain is typically induced by exertion, but is not observed whenb the subject is at rest.

Twenty-six non-smoking male subjects with stable angina pectoris were exposed to clean air and carbon monoxide, on two separate days, to determine if exposure to carbon monoxide reduced their ability to exercise, compared to clean air. Subjects were exposed for one hour, in a random crossover, double blind protocol, to either carbon monoxide (CO, 100 ppm) or to clean air. Subjects performed an incremental exercise stress test on a cycle ergometer until the point of onset of anginal pain. The subjects began the exercise test by pedaling the cycle at 0 watts workload for one minute, and then the workload was increased to 50 watts. The work rates were increased by 25 watts at 3 minute intervals. Blood samples were obtained before and after CO exposure and after the exercise test. Carboxyhemoglobin was determined in the blood samples using a spectrophotometric method (Instrumentation Laboratory Model 282 CO-Oximeter).

Measurements of minute ventilation, oxygen uptake, carbon dioxide expiration, and respiratory quotient were made, averaged over 30 second intervals and updated on a minute-by-minute basis. Heart rates and blood pressures were monitored during the last 30 seconds of each 3 minute exercise period. The time to onset of angina (TTA) and the duration of angina were also recorded.

The results indicate that CO exposure reduces exercise tolerance in people with angina even at the relatively low exposure levels achieved in this study. For the study group, taken as a whole, the 1 hr exposure to CO (100 ppm) resulted in an increase of carboxyhemoglobin from 1.5% (after clean air) to 2.8% (after CO) and the time to onset of angina was reduced by 6.9%, from 6.50 min to 6.05 min, respectively. The difference was significant in a 1-tailed paired "t"-test ($p=0.032$). The effect of CO exposure on subject's ability to exercise can be seen in Figure 1. The maximum exercise time for a subject after clean air was 12 minutes, but was 9 minutes after CO. The duration of angina was increased by 6.8%, from 1.46 min to 1.56 min, but this difference was not significant. Parameters related to exercise physiology and respiratory gas exchange exhibited changes indicating that CO exposure reduced the ability of subjects to exercise. The data are summarized in Tables 1 and 2. There was a negative correlation between a subject's body mass and the change in his time to onset of angina. This correlation appeared to relate to the finding that the percent change in COHb level following exposure was negatively correlated with body mass. We therefore separately analyzed data for subjects within 3 standard errors of the mean body mass (ie. subjects with body masses <95 kg). For these 19 subjects of mass 95 kg and below, carboxyhemoglobin levels were increased from 1.5 at baseline to 2.9 after the subjects breathed 100 ppm CO for 1 hour. The time to

angina was reduced by about 10%, which was significant, statistically ($p = 0.004$). The duration of angina pain was increased by about 10%. This change was not, however, statistically significant. The exercise physiology data showed decremental changes, however only the change in the rate of oxygen uptake (-3.2% approached significance; $p = 0.06$).

Subjects appeared to enter anerobic metabolism earlier in exercise after CO. Figure 2 shows the respiratory quotient (R) as a function of time during the exercise stress test. The R is higher on the CO day than on the clean air day for all but one of the data points and it begins its upward swing (typical of exercise) earlier on the CO day than on the clean air day.

The reduction of time to onset of angina in this study is similar to that reported by Andersen, et al. (1973) and by Aronow and Isbell (1973) for subjects with COHb levels raised to about 3%. Horvath reported that at 3.3% COHb, maximum oxygen uptake would be reduced by 4.9%; we find that the oxygen uptake (which is an index of aerobic power, or ability to do aerobic work) at the point of angina is reduced by 3.2% at a COHb of 2.9%. The data obtained in this study, although they are submaximal exercise tests since exercise was limited to onset of angina rather than to the overall stress of exercise, indicates a trend that confirms findings in normal subjects (Aronow and Cassidy, 1975) and subjects with chronic obstructive pulmonary disease (Aronow, et al., 1977).

Table 1 : Angina-Related Changes After Exposure to CO

	Time to Onset of Angina (min)		Duration of Angina (min)		Double Product* (bpm x mm Hg)	
DAY	Clean Air	CO	Clean Air	CO	Clean Air	CO
Subject						
1	6.50	5.42	2.00	2.75	22990.00	26368.00
2@	8.02	6.50	1.40	2.00	21168.00	20188.00
3	9.90	9.90	1.27	.05	20440.00	21996.00
4@	7.25	9.38	.63	.78	18400.00	18000.00
5	12.00	9.40	.47	.80	26384.00	24381.00
6	3.92	3.45	.58	.43	26574.00	25400.00
7	3.57	2.93	.58	.27	18156.00	19320.00
8	7.38	7.22	.35	.42	20952.00	12324.00
9	4.72	4.13	.80	1.03	24408.00	22440.00
10@	5.42	7.32	.65	1.12	13224.00	15770.00
11@	9.12	9.78	1.95	1.63	25740.00	26910.00
12	7.77	6.77	3.45	4.48	13904.00	15088.00
13	6.17	3.72	.97	.73	10920.00	9480.00
14	5.38	5.62	1.62	1.47	23120.00	22968.00
15	3.92	4.97	3.62	5.67	15438.00	14400.00
16@	5.43	4.33	2.67	2.20	11696.00	12354.00
17	8.25	8.88	2.05	2.87	12848.00	15390.00
18	8.03	7.02	1.08	.92	22736.00	22800.00
19@	3.67	3.68	1.03	1.85	15770.00	14940.00
20	4.40	2.20	1.18	.77	15120.00	12740.00
21@	5.72	6.25	3.05	1.67	12040.00	12264.00
22	6.38	5.45	.90	1.38	12556.00	12900.00
23	10.47	9.83	3.85	3.55	31174.00	30816.00
24	6.82	4.83	.62	.58	15092.00	14700.00
25	5.55	5.55	.45	.42	27510.00	25284.00
26	3.27	2.88	.68	.75	18360.00	15744.00
All Subjects(N)	26	26	26	26	26	26
Mean	6.50	6.05	1.46	1.56	19105	18652
s.d.	2.26	2.37	1.06	1.36	5744	5737
% Difference	-6.9%		+6.8%		-2.4%	
1-tailed "t" probability	0.032		0.232		0.167	
Subjects <95kg (N)	19	19	19	19	19	19
Mean	6.54	5.80	1.40	1.54	19930	19186
s.d.	2.45	2.41	1.11	1.57	5834	5981
% Difference	-11.3%		+10.0%		-3.7%	
1-tailed "t" probability	0.002		0.184		0.117	

Notes * Double Product = Heart Rate x Sys. Blood Press. (index of blood flow rate)
@Body mass >95 kg.

Table 2: Exercise Respiratory Physiology Data at the Angina Point

	Ventilation Rate (V_e Lpm)		Oxygen Uptake (VO2 Lpm)		CO_2 Elimination (VCO2 Lpm)	
DAY	Clean Air	CO	Clean Air	CO	Clean Air	CO
Subject						
1	51.5	48.3	1.10	1.18	1.23	1.29
2@	51.7	45.6	1.61	1.38	1.81	1.60
3	71.0	68.5	1.58	1.54	1.87	1.89
4@	43.0	55.7	1.30	1.46	1.41	1.73
5	82.5	62.6	1.59	1.48	1.75	1.55
6	48.8	42.9	1.06	.97	1.25	1.15
7	34.2	36.4	1.14	1.23	1.12	1.16
8	45.0	54.1	1.16	1.15	1.32	1.39
9	31.7	36.2	1.35	1.21	1.28	1.34
10@	47.3	55.0	1.23	1.34	1.34	1.46
11@	71.1	75.3	1.80	1.83	2.18	2.23
12	50.0	43.1	1.34	1.21	1.43	1.28
13	45.9	37.0	1.04	.91	1.43	1.23
14	36.7	38.6	1.21	1.25	1.35	1.41
15	30.0	36.6	1.10	1.19	1.09	1.28
16@	34.7	32.6	1.14	1.14	1.15	1.13
17	64.2	68.2	1.37	1.40	1.55	1.59
18	54.6	55.4	1.41	1.34	1.64	1.69
19@	42.0	40.9	1.15	1.15	1.17	1.14
20	48.4	38.2	1.09	1.04	1.12	.96
21@	44.5	52.0	1.40	1.34	1.58	1.63
22	57.2	55.6	1.22	1.15	1.48	1.40
23	50.1	50.9	1.55	1.56	1.87	1.81
24	52.1	40.1	1.26	1.24	1.49	1.26
25	48.2	46.3	1.07	1.09	1.42	1.40
26	30.5	29.0	1.16	.92	1.12	.95
All Subjects						
(N)	26	26	26	26	26	26
Mean	48.7	47.9	1.29	1.26	1.44	1.42
s.d.	12.9	11.9	0.20	0.21	0.28	0.30
% Difference	-1.6%		-2.3%		-1.4%	
1-tailed "t" probability	0.275		0.063		0.231	
Subjects <95kg						
(N)	19	19	19	19	19	19
Mean	49.1	46.7	1.25	1.21	1.41	1.37
s.d.	13.6	11.4	0.18	0.19	0.24	0.25
% Difference	-4.9%		-3.2%		-2.8%	
1-tailed "t" probability	0.079		0.032		0.079	

Note: @ Body mass >95 kg.

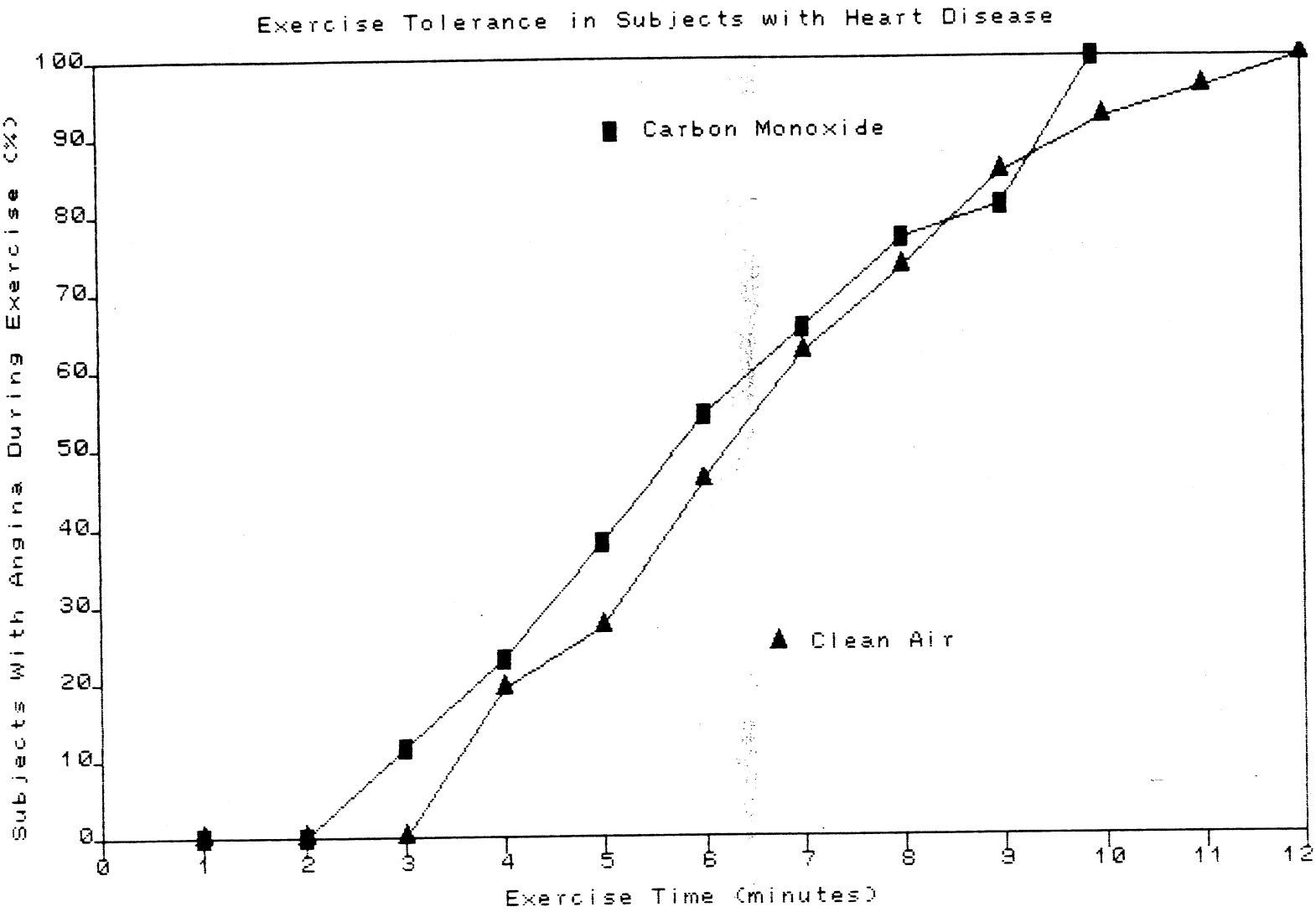

Figure 1. The ability of subjects with coronary artery disease to perform exercise is reduced relative to clean air by an earlier time to onset of angina pectoris.

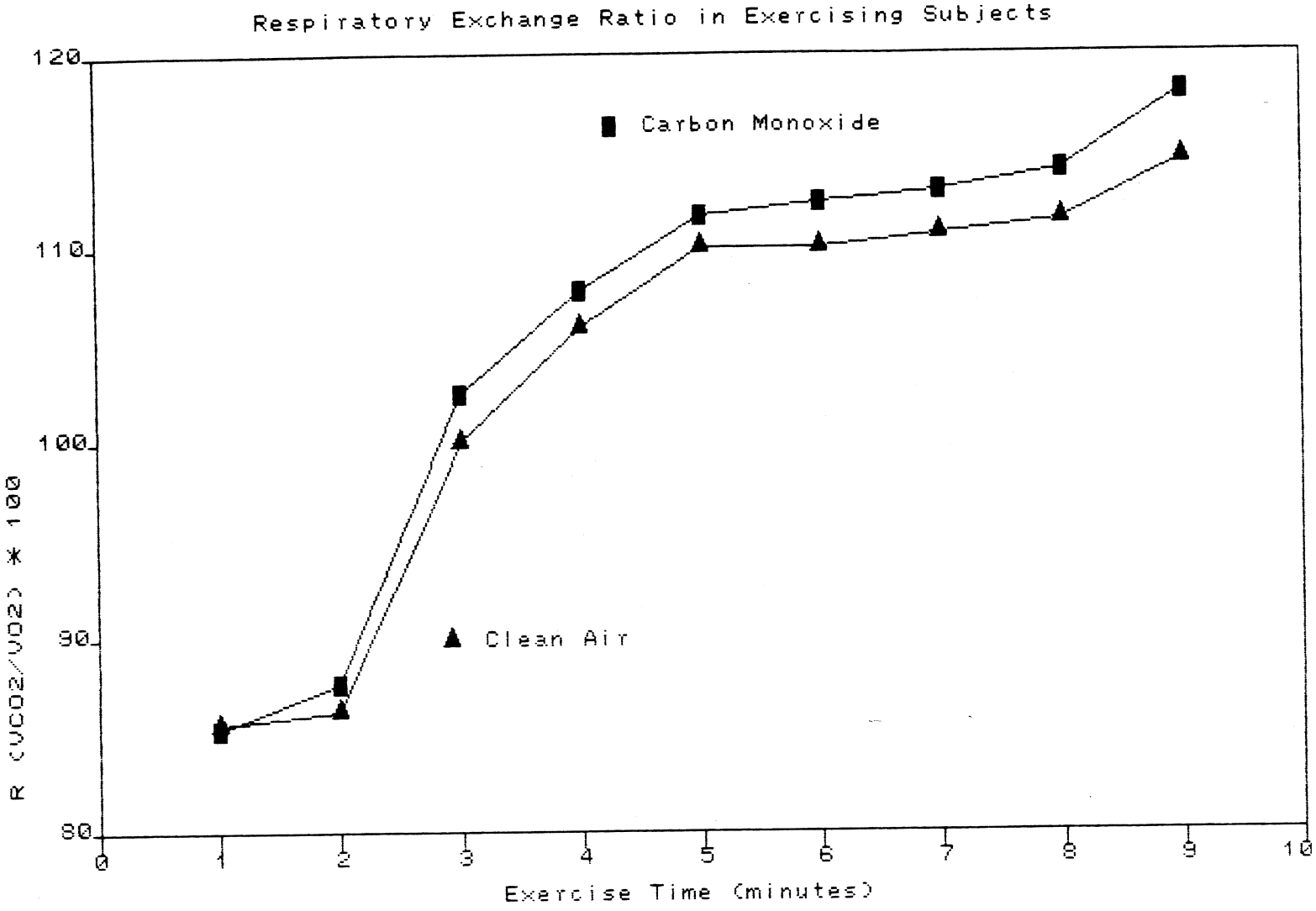

Figure 2. The respiratory exchange ratio indicates an earlier entry into anaerobic metabolism in subjects with coronary artery disease exposed to carbon monoxide, as compared with the same subjects exposed to clean air.

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