second stress test. The measurements revealed a post-exercise COHb of 2.0% ± 0.1% and 3.9% ± 0.1%, respectively. The time to onset of angina and the time to 1-mm ST-segment change were determined for each test. The percent changes following exposure at both 2% and 4% COHb were then compared with the same subject's response to the randomized exposure to room air.

When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST-segment change, exposure to CO levels producing COHb of 2% resulted in an overall statistically significant 5.1% decrease in the time to attain this level of ischemia. For individual centers, results were significant in one, borderline significant in one and nonsignificant in one. At 4% COHb, the decrease in time to the ST criterion was 12.1% (statistically significant for all patients; the effect was found in 49 of 62 subjects) relative to the air-day results. Significant effects were found in all three test centers. The maximal amplitude of the ST-segment change was also significantly affected by the CO exposures: at 2% COHb, the maximal increase was 11%, and at 4% COHb, the increase was 17% relative to the air day.

At 2% COHb, the time to angina was reduced by 4.2% in all patients (effects were significant in two test centers and nonsignificant in one center). At 4% COHb, the time was reduced by 7.1% in all patients (effects were significant in one, borderline significant in one, and nonsignificant in one center). The two end-points (time to angina and time to ST change) were also significantly correlated.

Only at 4% COHb, a significant reduction was found in the total exercise time and in the heart-rate blood-pressure product. (This double product provides a clinical index of the work of the heart and myocardial oxygen consumption.)

A number of other studies also evaluated the same end points. A reduced time to onset of exercise-induced chest pain was reported at a COHb of 2.5-3.0% (Aronow et al. 1972), 3% (Kleinman et al. 1989), 2.9%, 4.5% (Anderson et al. 1973), and 3.9% (Kleinman et al. 1998). No significant depression of the ST segment was found at a COHb of 3.8% (Sheps et al. 1987) and 3.9% (Kleinman et al. 1998). The differences in these studies has been explained (WHO 1999a) as differences in experimental methodology and analysis of data and as differences in subject populations and sample size.

Sheps et al. (1990; 1991) assessed the effect of CO exposure on ventricular arrhythmias. Forty-one subjects with established coronary artery disease (36 men and 5 women) with a mean age of 62.8 ± 1.1 years were analyzed. Patients were categorized based on arrhythmia frequency on the training day before, during, and 6 h after exercise: 10 had no arrhythmias (0-2 ventricular premature depolarizations (VPD)/h), 11 had low-level arrhythmias (3-50 VPD/h), 11 had intermediate-level arrhythmias (51-200 VPD/h), and 9 had high-level arrhythmias (>200 VPD/h). The protocol was performed over 4 consecutive days. Day 1 was the familiarization session and instructions were given on using the 24 h ambulatory electrocardiogram recorder. A symptom-limited maximal bicycle exercise test was also done. Days 2 to 4 were exposure days with either pure