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Atherosclerotic and Hypertensive Cardiovascular Disease are Associated with Death at Sublethal Carboxyhemoglobin Levels: A Postmortem Study

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Running head: CVD Associated with Sublethal COHb

ABSTRACT: Residential fires are a significant cause for morbidity and mortality in the United States. Death is often the result of soot and smoke inhalation causing carbon monoxide (CO) toxicity. The approximate lethal level of carboxyhemoglobin (COHb) in healthy adults has been well described. However, a significant number of medical examiner cases involve infirmed decedents, often elderly, with complex cardiovascular disease burdens. It is well known that death in these cases will occur at sublethal levels of COHb; however, increased lethality has been largely documented via anecdotal experience and lacks quantification. Fifty-five cases were identified where death resulted from smoke and soot inhalation suffered in a residential fire. The control group, with no cardiovascular disease, had an age-adjusted mean COHb level of 61.6% at the time of death. Presence of hypertensive cardiovascular disease showed a 30% reduction in COHb (age-adjusted mean 43.2%), atherosclerotic disease showed a 33% reduction (age-adjusted mean 41.5%), and combined disease presentation accounted for 41% reduction (age-adjusted mean 36.3%). When controlling for age, atherosclerotic and hypertensive cardiovascular diseases were each associated with statistically significant decreases in COHb ($p < 0.01$). Increasing age was associated with decreased COHb levels at 2.8% per 10 years of life ($p < 0.01$), even when modeled with hypertensive and atherosclerotic disease. These findings carry important public health significance, as well as practical significance for the medical examiner when interpreting COHb levels in cases of suspected deaths due to smoke and soot inhalation.

KEYWORDS: carbon monoxide, carboxyhemoglobin, cardiovascular disease, atherosclerosis, hypertension, residential fire, forensic pathology, autopsy

Despite continued public safety efforts, residential fires in the United States account for significant morbidity and mortality. The Federal Emergency Management Agency (FEMA) and the US Fire Administration recently reported residential building fires and losses in 2017. There were 371,500 fires

resulting in 2,695 deaths and 10,825 injuries, amounting to nearly $7.8 billion dollars in losses. In comparison to the preceding 10-year period (2008-2017), there was a 2% increase in fires and 8% increase in fire fatalities. Cooking related fires continue to be the leading cause of residential fires (52%) accounting for 170 fatalities and an 87% increase in deaths in the last 10-years. Unintentional or careless fires accounted for the largest portion of fire fatalities (435 deaths) with a 14% increase over the last 10-years.(1)

Previous studies have shown that the relative risk of injury and death in a residential fire is increased in men, in those impaired by alcohol or drugs, smokers, those who are disabled, and in the elderly.(2,3) A 2016 report of fire death from the National Center for Health Statistics and the US Census Bureau showed that individuals greater than the age of 55 account for nearly 60% of all fire fatalities and have a relative risk of fire death that increases precipitously from 1.1 at age 50 – 54 to 3.4 at ages greater than 84 years.

Fatalities due to residential fires are often due to inhalation of toxic gases with a minor contribution from cutaneous thermal injuries.(2,4) Approximately 25% of residential fire fatalities are due to thermal injuries alone, without a component of smoke and soot inhalation. Inhalation-related deaths are due to a complex mixture of gases and particulate matter volatilized by fire, colloquially referred to as smoke. The composition of smoke can vary dramatically depending on the materials that are burned, time from ignition, temperature, and oxygen supply.(5,6) However, the predominant toxic gases are consistently present, namely carbon monoxide (CO) (Table 1). Carbon monoxide is the major poisonous component in smoke produced by wood and polymer fires and is the cause of death is nearly all smoke inhalation-related deaths in residential fires. Carbon monoxide binds the heme group on hemoglobin, functioning as a competitive inhibitor of oxygen binding. Carbon monoxide binds with an affinity greater than 200-fold that of oxygen, forming carboxyhemoglobin (COHb), and effectively shutting down oxygen transport causing profound tissue hypoxia, blocking cellular respiration by binding to cytochrome-c oxidase, and resulting in chemical asphyxia and death.(7,8) The degree of carboxyhemoglobinemia is dependent on the relative amount of CO in the environment, duration of exposure, and respiratory rate. Normal COHb levels are <1%, while urban living and smoking cigarettes can account for up to levels of 10 – 15%. Levels above 30% are considered life threatening without intervention and greater than 50% is typically fatal (Table 2).

Several studies have suggested increased CO poisoning for individuals with cardiovascular disease causing death at reported sub-lethal concentrations compared with individuals without cardiovascular disease. One large study of greater than 500 fire fatalities found that 60% were due to CO poisoning alone, 20% were due to the effects of CO and cardiovascular disease, and only 11% of fatalities were due solely to thermal injuries.(9) In addition, it has been observed in both autopsy-based studies and studies of living patients that CO exposure can aggravate previously asymptomatic atherosclerotic and hypertensive cardiovascular disease, causing ischemic injury.(10–13) A study of living individuals with diagnosed angina pectoris found that while healthy adults could easily tolerate 10 – 15% COHb levels, individuals with coronary artery disease developed angina at concentrations as low as 2%.(11) Even low dose exposure can have significant effects on cardiac function in populations with coronary artery disease burdens.(14,15)

Acute myocardial injury is common among individuals exposed to CO.(12,13) A retrospective study of 230 individuals with moderate to severe CO poisoning found evidence of myocardial ischemia in one-third of cases.(13) Exposure to levels of 15% COHb is sufficient to cause myocardial infarction in individuals with at least moderate cardiovascular disease.(11)

For medical examiners, it can be challenging to reconcile the roles of competing factors in the determination of cause and manner of death. Although the role of chronic disease is well known, the interplay of fire and disease is difficult to untangle, and a true autopsy-based study of the relationship between cardiac co-morbidities and CO poisoning has not been identified in the literature. The ability to anticipate the effect of specific cardiovascular findings in relation to CO poisoning may be of great benefit when opining the cause and manner of death.

In order to further characterize the relationship between atherosclerotic and hypertensive cardiovascular disease and CO poisoning, COHb level and autopsy findings of decedents who died as a result of smoke and soot inhalation in residential fires were examined. It was hypothesized that decedents with cardiac comorbidities would have greater susceptibility to CO poisoning, manifesting as lower postmortem COHb levels.

Methods

Inclusion Criteria

Cases were obtained using CaseManager$_{fw}$™ (QuincyTech, Woodbridge, CT) software system in the Wayne County Medical Examiner's Office. We included cases with complete autopsy examinations of individuals whose death was certified as smoke and soot inhalation, in which thermal injuries were not deemed to be contributory to the cause of death and were not included in the immediate cause of death. Routine histology was not examined in these cases. All cases had COHb levels determined via postmortem toxicology. Hydrogen cyanide toxicity was not suspected in any cases and postmortem samples were not examined for hydrogen cyanide. Children were excluded from the study. Cases that were confounded by additional trauma or other injuries were excluded. There were 55 cases identified that met the preceding criteria (from 2007 to 2019).

Data Collection

The autopsy reports were reviewed for relevant demographic data, cause and manner of death, and autopsy findings. Autopsy reports and postmortem photographs were examined for the presence of soot in the airways, severity of thermal injuries, and the presence of cardiovascular disease. Cardiovascular disease was recorded as either atherosclerotic or hypertensive. Atherosclerotic disease was categorized based on narrowing of the coronary artery diameter by greater than 50% (equivalent to 75% luminal stenosis) in any coronary artery.(16) Hypertensive cardiovascular disease was categorized based on the presence of cardiomegaly and concentric left ventricular hypertrophy (> 1.5 cm), in the absence of other explanations for concentric left ventricular hypertrophy.(17) Height and weight recorded at the time of death were used to calculate the body mass index (BMI). The heart weight recorded at the time of autopsy and BMI were used to identify decedents with cardiomegaly, based on parameters previously published.(18,19) Decedents with no cardiovascular disease were recorded as controls.

Postmortem toxicology was collected on all cases. Peripheral blood from the iliac vein was used.(20) Toxicology prior to 2012 was performed at the toxicology laboratory at the Wayne County Medical Examiner's Office. Toxicology testing after 2012 was submitted to National Medical Services (NMS labs, Horsham, PA). Samples were tested for carbon monoxide exposure by quantification of COHb using a bio-uptake screen via spectrophotometry (5% reportable limit) and confirmed on gas chromatography/mass spectrometry (2% reportable limit).

Statistical Analysis

Individuals were categorized into one of four categories: (1) controls; (2) hypertensive cardiovascular disease (HCVD); (3) atherosclerotic cardiovascular disease (ASCVD); and (4) hypertensive and atherosclerotic cardiovascular disease (HASCVD). Baseline demographic characteristics and autopsy findings for controls and patients with subgroups of cardiovascular pathology were compared. To evaluate for possible confounding variables, statistically significant differences between the two groups were assessed using a one-way analysis of variance (ANOVA) for continuous variables and a chi-squared test for categorical variables.

Variation in COHb level between the four groups was assessed using an analysis of covariance (ANCOVA), including age as a covariate and with an a priori alpha of $p < 0.05$ for statistical significance. The ANCOVA subgroups were assessed for normality using visual evaluation of a Q-Q plot and for homogeneity of variances using Levene's test. Pairwise comparisons between individual groups were performed with a Tukey range test with corrected p values. To evaluate the relative roles of age, hypertensive cardiovascular disease, and atherosclerotic cardiovascular disease, these three variables were modeled together in a multivariate linear regression.

To screen for other possible associations with COHb levels, univariate linear regressions were performed with sex, race, BMI, heart weight, and cardiomegaly as independent variables. Because it was hypothesized that BMI may have a non-linear (e.g. J-shaped) relationship with COHb levels, BMI was grouped into three subgroups and analyzed by one-way ANOVA.

Results

There were 55 cases identified that met criteria for inclusion into the study. Demographically, the mean age was 56.0 years, 64% of decedents were men, and 60% were black. The mean heart weight was 430 grams and 65% had cardiomegaly, as defined by previously published criteria.(18,19) Nearly all of the decedents had soot in the airways (96%) and a majority had thermal injuries (78%).

There were 23 decedents (42%) with no cardiovascular disease at autopsy used as controls. Of the remaining 22 cases, all decedents had cardiovascular disease confirmed at autopsy. There were 8 (15%) cases identified with hypertensive cardiovascular disease (HCVD), 11 (20%) with atherosclerotic cardiovascular disease (ASCVD), and 13 (24%) with both atherosclerotic and hypertensive cardiovascular disease (HASCVD).

By one-way ANOVA analysis, the subgroups of disease significantly differed in age ($F(3,51) = 12.6$, $p < 0.01$) and heart weight ($F(3,51 = 14.7$, $p < 0.01$). By chi-squared analysis, cardiomegaly significantly differed between groups ($p = 0.01$) (Table 3). There were no other statistically significant differences between subgroups in terms of autopsy findings or demographic characteristics. Because cardiomegaly and heart weight were incorporated into our definition of hypertensive cardiovascular disease, only age was included as a covariate in further analysis of COHb between subgroups.

ANCOVA analysis showed statistically significant differences in mean age-adjusted COHb levels between subgroups. ($F(3, 50) = 16.8$, $p < 0.01$). Mean age-adjusted COHb levels were as follows: in the control group, 62% (95% CI = 57% to 66%); in the HCVD group, 43% (95% CI = 36% to 51%); in the ASCVD group, 42% (95% CI = 35% to 48%); and in the HASCVD group, 36% (95% CI = 30% to 42%). (Figure 1) By pairwise adjusted analysis, all groups were significantly lower than normal controls, but did not significantly differ among each other. COHb values for the subgroups were normally distributed based on visual interpretation of a Q-Q plot and met the assumption of homogeneity of variances based on Levene's test ($p = 0.31$).

Univariate Linear regression showed no statistically significant association with COHb levels and body mass index (BMI). We further subgrouped BMI into three groups: less than 20, 20-30, and greater than 30. By one-way ANOVA, no statistically significant association was seen between BMI subgroups and COHb levels (Figure 2).

When modeled together controlling for the presence of hypertensive cardiovascular disease and atherosclerotic cardiovascular disease (independent of specific cardiovascular disease subgroup), increasing age showed a linear relationship with decreasing COHb levels ($r^2 = 0.66$), with each 10 years of life associated with a 2.8% decrease in COHb levels (95% confidence interval = 0.9% to 4.6%, $p < 0.01$) (Table 4). In this model, the presence of hypertensive cardiovascular disease was associated with a mean decrease of 11.8% COHb (95% CI = 5.8% to 17.9%), and atherosclerotic cardiovascular disease was associated with a mean decrease of 14.8% (95% CI = 7.1% to 22.4%).

Additionally, we performed univariate linear regression to screen for other variables that may be associated with decreased COHb levels. No statistically significant associations were observed between

COHb levels and race (p = 0.79), sex (p = 0.44), or cardiomegaly (p = 0.10). A statistically significant association was observed between COHb levels and heart weight, but this association did not remain after controlling for the presence of hypertensive cardiovascular disease (p = 0.74). When men and women who met criteria for cardiomegaly based on BMI were compared with sex-matched controls, there was no significant difference identified between the two groups.

Discussion

Residential fire fatalities continue to be a significant cause of death in the United States. Death is usually caused by smoke and soot inhalation, with resulting CO poisoning. The association between cardiovascular disease and CO poisoning has been shown in various clinical studies to cause angina and increase the risk of myocardial infarction.[11],[14,15] Further characterization of the effect of specific cardiovascular pathologies, namely atherosclerotic and hypertensive disease, and their effect on fatal CO poisoning was lacking.

Consistent with previous reports, decedents with cardiovascular disease burdens had reduced COHb levels at the time of death when compared with controls. All three subgroups of cardiovascular disease – HCVD, ASCVD, and HASCVD – showed significant decreases in age-adjusted COHb levels compared with controls. These findings are consistent with previous literature establishing that patients with atherosclerotic and hypertensive cardiovascular disease show increased vulnerability to CO poisoning.[11,14,21]

BMI, which has repeatedly been shown to be a reliable health indicator for cardiometabolic risk factors[22] such as hypertension, hypercholesterolemia, and inflammation, was not associated with decreased COHb levels. In addition, cardiomegaly and heart weight were not independently associated with decreased COHb levels once hypertensive disease controlled. These findings further support the unique role for hypertensive and atherosclerotic disease – rather than measures of overall cardiometabolic health – in increasing the risk of fatal CO poisoning.

The strong association between increased age and decreased postmortem COHb levels strongly supports the substantial vulnerability of elderly individuals. Previous literature has shown that the elderly are at increased risk of death due to residential fire, and the findings in this study show that increased susceptibility to CO poisoning accounts for some component portion of that risk with other

risk factors being debility/disability hindering any potential evacuation of hazardous environments. (2,3)

However, our multivariate analysis shows a striking predominance for the impact of cardiovascular disease when compared with the impact of age. The impact of age, likely due to the cumulative effect of degenerative vascular and organ disease, was equivalent to a reduction of COHb concentration of ~2.8% per decade of life. The analysis shows that the presence of hypertensive disease is the risk equivalent to ~42 additional years of life. The presence of atherosclerotic disease is the risk equivalent to ~53 additional years of life. For example, a 90 year old healthy decedent would be expected to have roughly the same fatal COHb level as a 48 year old decedent with hypertensive cardiovascular disease or a 37 year old decedent with significant atherosclerosis.

Nonetheless, age is a complex factor. The fact that increasing age is associated with decreased COHb levels, independent of cardiovascular disease, suggests that other age-related factors play a smaller role in CO poisoning. These factors may include other co-morbid conditions, including those affecting renal, hepatic, and pulmonary function, limitations on physical activity, or limited ability to function independently. The role of confounding parameters was not evaluated in this study. Our findings show that age and cardiac comorbidities account for a majority of the variability in CoHb levels. The precise degree to which other comorbidities may affect COHb levels remains undefined. Based on the findings of our multivariate regression, up to 34% of the variation in COHb is not explained by the variables that were assessed. For example, pulmonary disease (e.g. chronic obstructive pulmonary disease) may contribute to a reduced COHb level, but was not assessed in this study.

The findings here carry important practical significance for the medical examiner as well as important public health implications. The effect of cardiovascular disease on fire fatality is significant, and it accounts for significantly lower levels of COHb observed at autopsy and postmortem toxicology. When significant disease is not identified in the setting of sub-lethal COHb, the contribution of senescence should be considered with care and other factors (such as exposure to hydrogen cyanide, another toxic smoke product) should be investigated. While our study did not evaluate the role of hydrogen cyanide, further research could explore the relationship between hydrogen cyanide toxicity, cardiovascular disease, and fatal COHb levels. When establishing cause and manner of death, it is important to

recognize that commonly cited figures of fatal COHb levels will likely not be applicable when decedents have significant underlying cardiovascular disease.

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Toxic Gas	Common Sources
Carbon monoxide (CO)	Organic Material
Nitrogen dioxide	Wood
Hydrogen chloride	Plastics
Hydrogen cyanide	Wool, silk, nylons, polyurethane, rubber
Benzene	Petroleum products
Aldehydes (various)	Wood, cotton, paper
Ammonia	Nylon

TABLE 1—*Toxic gas components of wood and polymer smoke. Smoke is a complex mixture of gases, many of which are toxic. (23) Toxic gases are categorized as either asphyxiants, such as CO or hydrogen cyanide, or as irritants such as hydrogen chloride or nitrogen dioxide.*

COHb level (%)	Symptoms
0 - 10%	Well tolerated, minimal effects
10 - 30%	Visual impairment, headache, palpitation, dyspnea
30 - 50%	Somnolence, unconsciousness, life threatening
>50%	Coma, imminent death

TABLE 2—*Carbon monoxide toxicity based on carboxyhemoglobin level. Severe poisoning by CO results in marked hypotension and lethal arrhythmias, which have been considered responsible for the majority of fire deaths. Adapted from Carbon Monoxide Acute Exposure Guideline Levels. In: Acute Exposure Guideline Levels for Selected Airborne Chemicals. Washington, DC: National Academies Press, 2010;49–143.*

	All cases	Controls	HCVD	ASCVD	HASCVD	p-value
Number of cases	55	23	8	11	13	
Demographics						
Age, mean (yrs) ± SD	56.0 ± 19.4	46.0 ± 17.2	43.4 ± 11.4	71.6 ± 16.6	68.2 ± 12.4	**< 0.01**
Male (%)	35 (64)	15 (65)	7 (88)	6 (55)	7 (54)	0.40
Black (%)	33 (60)	15 (65)	4 (50)	8 (73)	6 (46)	0.56
Autopsy Findings						
Mean % COHb ± SD	48.9 ± 17.4	64.4 ± 10.8	46.8 ± 15.9	37.2 ± 9.3	32.8 ± 8.0	**< 0.01**
BMI ± SD	25.8 ± 7.3	24.7 ± 6.1	28.7 ± 9.7	24.5 ± 8.1	27.2 ± 7.3	0.59
Heart weight, mean (grams) ± SD	430 ± 121	359 ± 54	525 ± 88	366 ± 62	550 ± 132	**< 0.01**
Cardiomegaly (%)	36 (65)	11 (48)	6 (75)	6 (75)	13 (100)	**0.01**
Soot in the airway (%)	53 (96)	22 (96)	8 (100)	10 (91)	13 (100)	0.62
Thermal injury (%)	43 (78)	19 (83)	6 (75)	6 (55)	12 (92)	0.14

HCVD = Hypertensive cardiovascular disease; ASCVD = Atherosclerotic cardiovascular disease; HASCVD = Hypertensive and atherosclerotic cardiovascular disease

TABLE 3—*Baseline demographic characteristics and autopsy findings for controls and decedents with cardiovascular disease. Statistical significance was assessed using one-way ANOVA for continuous variables (age, COHb level, BMI, and heart weight) and using a chi-squared test*

for categorical variables (sex, race, cardiomegaly, soot in airways, and thermal injuries).

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| Factor	Reduction in COHb level (%)	95% CI (%)
10 years of age	-2.8	-0.9 to -4.7
HCVD	-11.8	-5.7 to -17.9
ASCVD	-14.8	-7.1 to -22.4

TABLE 4—*Relative contributions of age, hypertensive cardiovascular disease, and atherosclerotic cardiovascular disease to carboxyhemoglobin level. All values were obtained using multivariate linear regression with carboxyhemoglobin (COHb) as the dependent variable.*

Figure Legends

FIG. 1—*Association between carboxyhemoglobin level and cardiovascular disease. Comparison of COHb levels between cardiovascular disease subgroups using an ANCOVA analysis with age as a covariate showed a significant difference between groups. (F(3, 50) = 16.8, p < 0.01). Pairwise comparisons between groups were performed by post-hoc testing with Tukey correction.*

HCVD = Hypertensive cardiovascular disease; ASCVD = Atherosclerotic cardiovascular disease; HASCVD = Hypertensive and atherosclerotic cardiovascular disease

FIG. 2—*Association between body mass index and carboxyhemoglobin level. No statistically significant association between BMI and COHb level was seen either in linear regression (p = 0.58) or when stratified by BMI groups and analyzed by one-way ANOVA (F(2, 52) = 1.1, p = 0.36).*
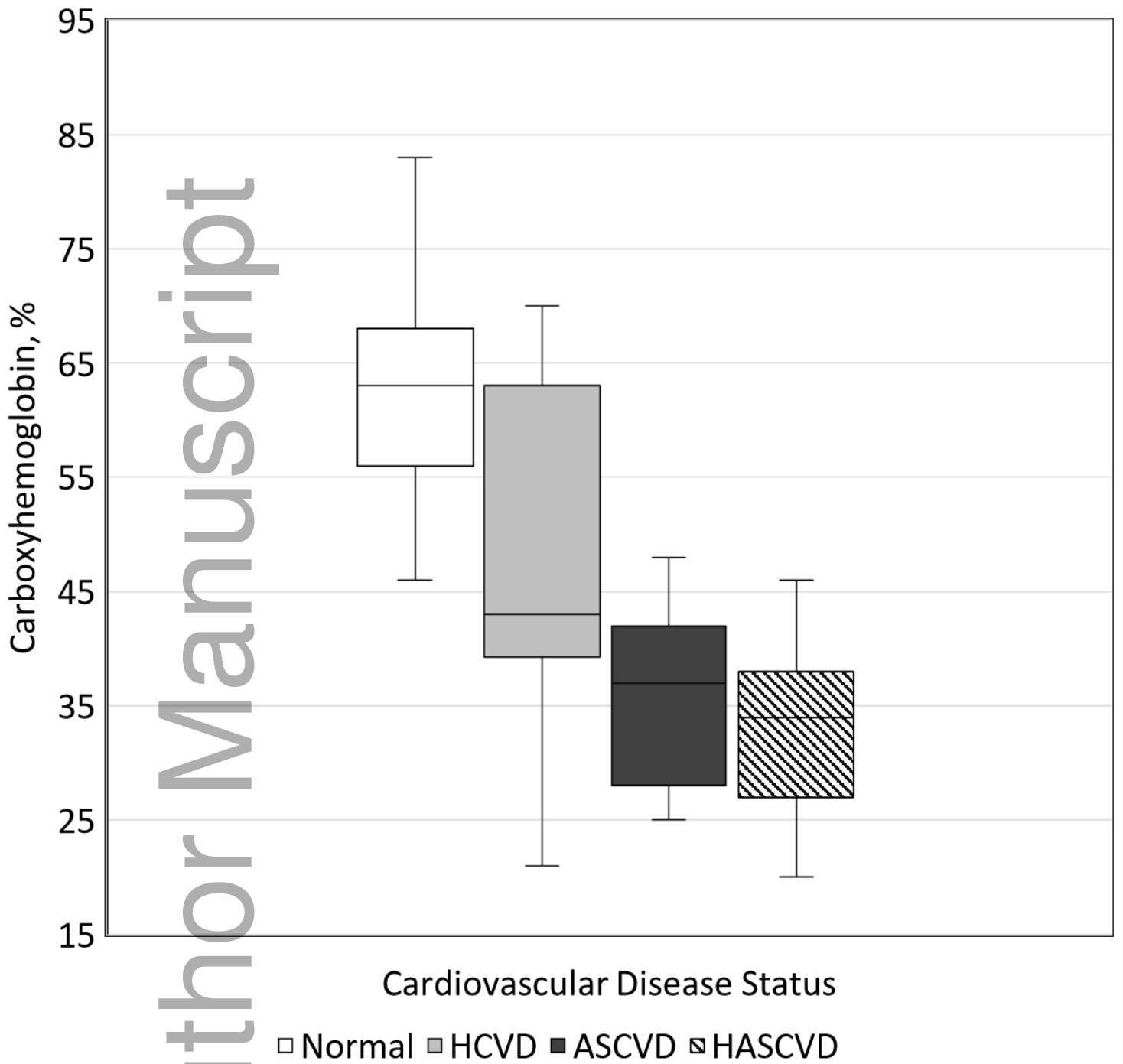
	Normal	HCVD	ASCVD	HASCVD
Number of cases	23	8	11	13
Unadjusted mean COHb (%)	64.4	46.8	37.2	32.8
Standard deviation	10.8	15.9	9.2	8.0
Age-adjusted mean COHb (%)	61.6	43.2	41.5	36.3
P-Values				
vs. Normal		<0.01	<0.01	<0.01
HCVD vs HACVD		0.52		0.52
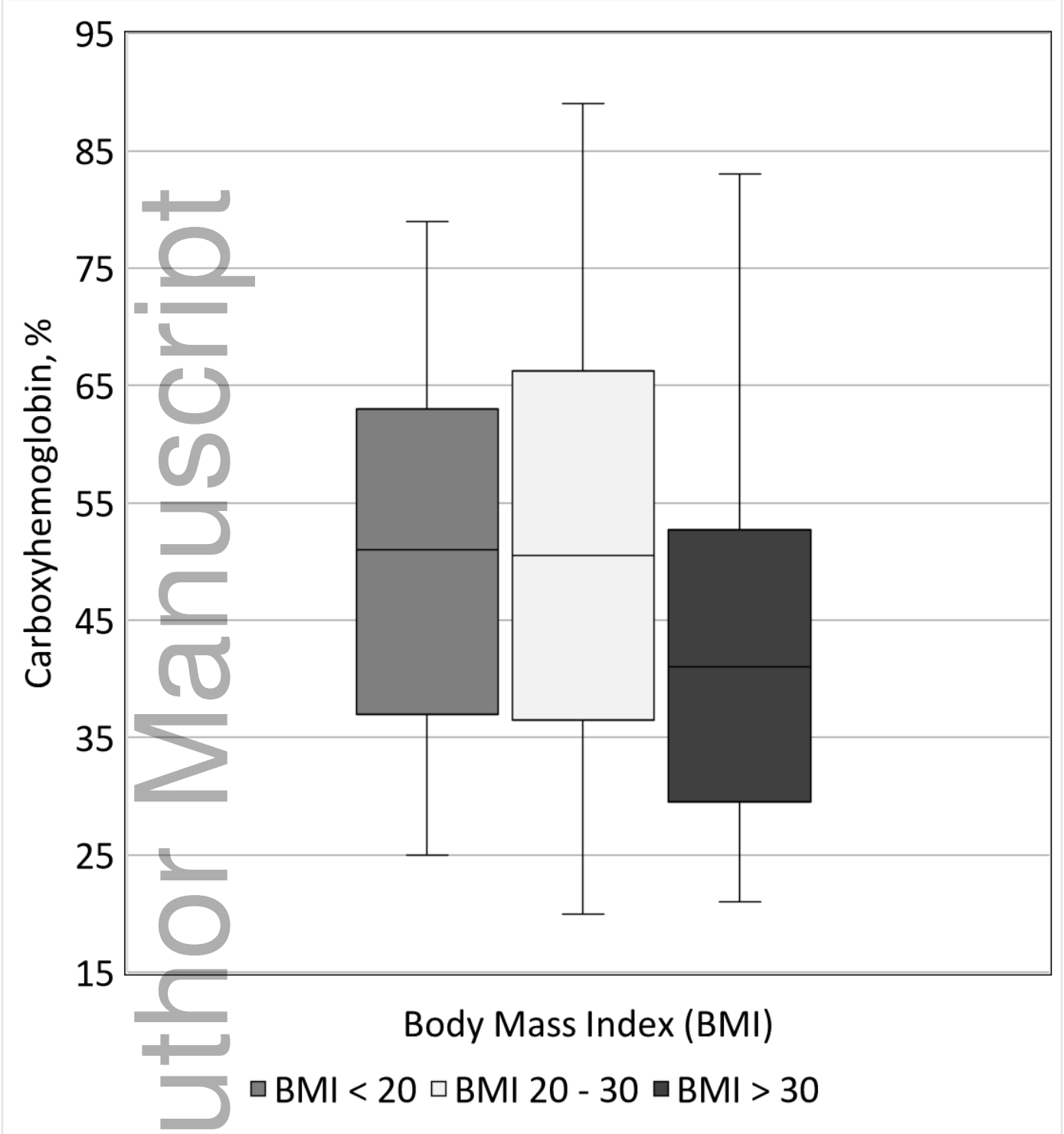
	BMI < 20	BMI 20 − 30	BMI > 30
Number of cases	15	26	14
Mean COHb (%)	49.5	50.6	41.2
Standard deviation	15.4	18.46	18.0
P-values (vs BMI 20 − 30)		0.85	0.17