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# Risk of Peripheral Artery Disease in Patients With Carbon Monoxide Poisoning

## *A Population-Based Retrospective Cohort Study*

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**Abstract:** Carbon monoxide (CO) poisoning can cause several life-threatening complications, particularly in cardiovascular and neurological systems. However, no studies have been performed to investigate the association between peripheral artery disease (PAD) and CO poisoning. We constructed a population-based retrospective cohort study to clarify the risks between PAD and CO poisoning.

This population-based cohort study involved analyzing data from 1998 to 2010 obtained from the Taiwanese National Health Insurance Research Database, with a follow-up period extending to the end of 2011. We identified patients with CO poisoning and selected a comparison cohort that was frequency matched according to age, sex, and year of diagnosis of CO poisoning at a ratio of 1 patient to 4 control patients. We analyzed the risks for patients with CO poisoning and PAD by using Cox proportional hazards regression models.

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In this study, 9046 patients with CO poisoning and 36,183 controls were included. The overall risks for developing PAD were 1.85-fold in the patients with CO poisoning compared with the comparison cohort after adjusting for age, sex, and comorbidities.

Our long-term cohort study results showed a higher risk for PAD development among patients with CO poisoning.

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**Abbreviations:** CI = confidence interval, CO = carbon monoxide, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, PAD = peripheral artery disease, SD = standard deviation.

## INTRODUCTION

Carbon monoxide (CO) poisoning is a crucial public health problem and results in a high health burden. Recent data have shown a 16.7% annual average mortality rate among patients with unintentional CO poisoning in the United States between 1999 and 2004. According to records from 2007, among patients with confirmed CO poisoning, 21,304 patients visited emergency rooms, and 2302 patients were hospitalized.<sup>1</sup> The major toxicological effects of CO could result from CO's absolute higher binding affinity to hemoglobin than oxygen. This could lead to tissue hypoxemia as well as further oxidative stress and then to free-radical-formation-related tissue damage, inflammation, and apoptosis.<sup>2-4</sup>

In cardiac and neurological systems, high oxygen is frequently required to maintain organ and tissue function. CO poisoning typically causes severe damage to these systems and subsequent acute and long-term sequelae.<sup>5</sup> Most complications resulting from CO poisoning are severe cardiac or neurological complications such as cardiac arrhythmia, myocardial injury, cerebral ischemic infarction, or hemorrhagic events.<sup>6,7</sup> Although most studies of CO poisoning have focused on neurological sequelae, such as persistent and delayed neurological sequelae, cardiovascular system sequelae, including cardiac dysfunction and myocardial injury, may also be considered.<sup>8-10</sup> A recent large-sample-size study also clarified the relationship between CO and cardiac events including cardiac arrhythmia and myocardial infarction.<sup>11</sup> Several possible mechanisms have been established, including tissue and myocardium hypoxia and damage, vascular endothelial dysfunction, and further atherosclerosis processes.<sup>12,13</sup>

Peripheral artery disease (PAD) is a common circulatory disease, which impairs adequate blood flow to peripheral tissue and causes tissue damage. On the basis of previous data in Taiwan, the prevalence of PAD was 4.3% to 5.4% in general

population during the period from 2000 to 2010.<sup>14,15</sup> The major pathophysiology of PAD is atherosclerosis processes, and conventional risk factors for PAD include smoking, older age, DM, HTN, hyperlipidemia, CKD, and chronic obstructive pulmonary disease (COPD).<sup>16</sup> PAD is an atherosclerotic process, which is involved in noncoronary arteries such as those in the lower extremities. However, no recent studies have demonstrated the relationship between CO poisoning and PAD.<sup>10</sup> Therefore, this population-based retrospective cohort study used data from a representative health insurance database to clarify the relationship between CO poisoning and PAD.

## METHODS

### Data Source

A longitudinal cohort study was established based on the Taiwanese National Health Insurance Research Database (NHIRD), which contains information regarding hospital admissions of all insurants in Taiwan. Taiwan began the National Health Insurance (NHI) program in 1995, and 99% of Taiwan's 23.74 million residents are covered. The details of the program have been well recorded in previous studies.<sup>17</sup> The NHIRD is used for administrative and research purposes, and before electronic files are released, personal identification information is encrypted to protect patient privacy. Diagnostic codes in the NHIRD are according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to exempt from requiring informed consent by the Institutional Review Board of China Medical University and Hospital (CMUHIO4-REC2-115).

### Sampled Patients

In the period from 2000 to 2011, adult patients diagnosed with CO poisoning (ICD-9-CM code 986) were included in the CO poisoning cohort. The date of first hospitalization for CO poisoning was identified as the index date. Patients with a history of PAD (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9) before the index date, younger than 20 years old, and those with incomplete information were excluded. All remaining patients without a history of PAD from the entire NHIRD were included. The patients without CO poisoning were frequency-matched with the CO poisoning cases at a ratio of 4:1 by age (in 5-y bands), sex, and the year that CO poisoning was diagnosed.

### Outcome

The outcome of this study was a new diagnosis of PAD. In Taiwan, the defined diagnosis of PAD was based on imaging studies such as angiography, magnetic resonance angiography, or computed tomography angiography. Besides, the diagnostic codes in NHIRD were examined by 2 and more specialists to confirm the diagnostic accuracy. All data of which were obtained from hospital records. The follow-up period was the period from the index date until the date of PAD diagnosis, the date of withdrawal from the database, or the date of the end of follow-up (December 31, 2011), whichever occurred first.

### Comorbidities

All comorbidities including diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM code 272), heart failure (ICD-9-CM code 428), and

smoking-related diseases [including asthma (ICD-9-CM code 493), COPD (ICD-9-CM codes 491, 492, 496), coronary artery disease (CAD) (ICD-9-CM codes 410-414), and stroke (ICD-9-CM codes 430-438)] were determined from inpatient claims data for each patient and defined as preexisting comorbidities if they were claimed prior to the index date. Hyperbaric oxygen (HBO) therapy (Procedure Code 93.95) administered to CO poisoning patients was considered a severity indicator.

### Statistical Analysis

The distributions of age, sex, and comorbidities were compared between the CO poisoning and non-CO poisoning cohorts by using a  $\chi^2$  test. A Student *t* test was used to examine the mean ages and mean follow-up years between both cohorts. The cumulative incidence of PAD was assessed using the Kaplan–Meier method in the CO poisoning and non-CO poisoning cohorts, with significance based on the log-rank test. The incidence density rates of PAD between the 2 cohorts were calculated and stratified by sex, age, comorbidity, and follow-up years. Univariate and multivariate Cox proportional hazards regression analyses were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of PAD development in the CO poisoning cohort compared with the non-CO poisoning cohort. Multivariate models were simultaneously adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, and stroke. The entire matching procedure and all statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC). A 2-tailed  $P < 0.05$  was considered significant.

## RESULTS

Our study cohort consisted of 9046 patients with CO poisoning and 36,183 patients without CO poisoning. Most patients were 20 to 34 years of age (42.8%) and men (52.6%) (Table 1). The mean age ( $\pm$  standard deviation [SD]) of the CO poisoning and non-CO poisoning cohorts was  $39.8 \pm 14.3$  and  $39.9 \pm 13.9$  years, respectively. Compared with the non-CO poisoning cohort, more comorbidities at the baseline were observed in the CO poisoning cohort ( $P < 0.001$ ). The mean follow-up duration was  $4.53 \pm 3.15$  years in the CO poisoning cohort and  $4.94 \pm 3.03$  in the non-CO poisoning cohort. The Kaplan–Meier plot in Figure 1 illustrates that the cumulative incidence for developing PAD was higher in the CO poisoning cohort than in the non-CO poisoning cohort (log-rank test  $P < 0.001$ ).

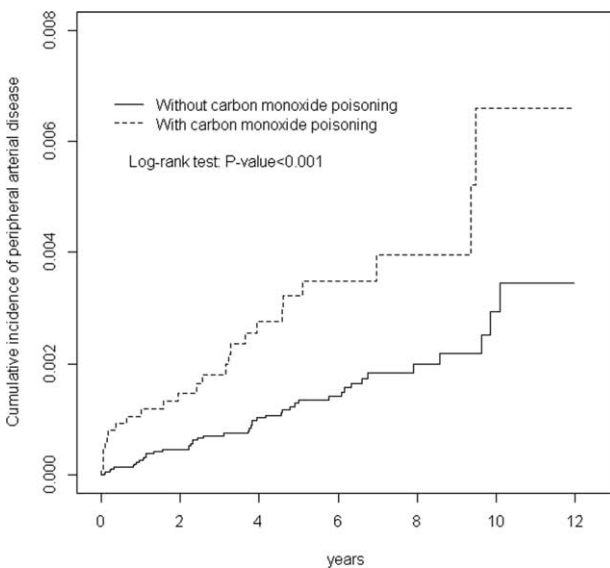
The overall incidence of PAD was significantly higher in the CO poisoning cohort than in the non-CO poisoning cohort (6.10 vs 2.57, respectively, per 1000 person-years) with an adjusted HR = 1.85 (95% CI = 1.12–3.06) (Table 2). The sex-specific incidence for women and men in the CO poisoning cohort was 4.89 and 7.29 per 1000 person-years, respectively. There was higher risk for developing PAD in women in the CO poisoning cohort than women without CO poisoning cohort (adjusted HR = 2.43, 95% CI = 1.07–5.53). The age-specific incidence of PAD increased with age in the CO poisoning and non-CO poisoning cohorts. Patients younger than 49 years old with CO poisoning had a 3.25-fold higher risk of PAD than the control group in the non-CO poisoning cohort (95% CI = 1.28–8.27). In comparison with the non-CO poisoning cohort, the risks of PAD in the CO poisoning cohort were significantly higher in patients without any comorbidities (adjusted HR = 3.27; 95% CI = 1.58–6.78).

**TABLE 1.** Characteristics of Patients With Carbon Monoxide Poisoning and Matched Patients Without Carbon Monoxide Poisoning

	Carbon Monoxide Poisoning				P Value
	Yes (N = 9046)		No (N = 36,183)		
	n	%	n	%	
Age, y					0.99
≤34	3873	42.8	15,492	42.8	
35–49	3358	37.1	13,432	37.1	
≥50	1815	20.1	7259	20.1	
Mean (SD)*	39.8	14.3	39.9	13.9	0.50
Sex					0.99
Female	4289	47.4	17,155	47.4	
Male	4757	52.6	19,028	52.6	
Comorbidity					
Diabetes	590	6.52	762	2.11	<0.001
Hypertension	852	9.42	1280	3.54	<0.001
Hyperlipidemia	323	3.57	406	1.12	<0.001
Heart failure	115	1.27	175	0.48	<0.001
Smoking-related diseases					
Asthma	244	0.67	191	2.11	<0.001
COPD	181	2.00	277	0.77	<0.001
CAD	432	4.78	551	1.52	<0.001
Stroke	356	3.94	545	1.51	<0.001

χ<sup>2</sup> test.  
\* Student t test.

Table 3 shows the joint effects of CO poisoning and either comorbidity or HBO therapy on the risk of PAD. The patients with CO poisoning and comorbidity were at a much higher risk of PAD than patients without CO poisoning and comorbidity (adjusted HR = 6.27, 95% CI = 3.10–12.7) (Table 3).



**FIGURE 1.** Cumulative incidence of peripheral artery disease among patients with and without carbon monoxide poisoning.

Compared with patients without CO poisoning and HBO therapy, patients with CO poisoning and HBO therapy were 4.56-fold more likely to develop PAD (95% CI, 2.05–10.1), followed by 2.23-fold more likely to develop PAD in patients with CO poisoning and without HBO therapy (95% CI = 1.29–3.84).

The incidence for developing PAD decreased with the follow-up time in the CO poisoning cohort in stratified analysis by follow-up duration (Table 4). There was higher risk for developing PAD in the CO poisoning cohort than the non-CO poisoning cohort with a ≤3-year follow-up (adjusted HR = 1.08, 95% CI = 1.05–1.10).

### DISCUSSION

This is the first population-based cohort study to elucidate the association between PAD and CO poisoning by using a large database and adjusting for traditional PAD risk factors including diabetes, hypertension, hyperlipidemia, asthma, and COPD. This study concludes that there was higher risk for subsequently developing PAD in patients with CO poisoning. In our study, this risk was increased 1.85-fold in the CO poisoning cohort compared with the control groups after adjusting for age, sex, and comorbidity. According to our study results, the incidence rate of PAD was higher in the patients with CO poisoning and chronic medical comorbidities than among the general population without chronic comorbidities. In addition, ICD-9 coding HBO therapy was used as a severity guide of CO poisoning in patients. In this study, the CO poisoning patients, regardless of whether they received HBO therapy, had a higher incidence rate of PAD than the general population. With a mean follow-up period of 4.53 years, the risk of PAD development in patients with CO poisoning appeared primarily within the first 3 follow-up years, and the incidence of PAD declined after the first 3 years.

Several potential pathophysiologies may elucidate the association between PAD and CO poisoning. First, CO connects to hemoglobin irreversibly with a binding affinity 200 to 400 times higher than that of CO to oxygen, which causes tissue hypoxia and damage.<sup>18</sup> Schneiderman et al showed that CO is an atherogenic factor, which results from arterial luminal blood and vasa vasorum chronic hypoxemia.<sup>19</sup> In addition, Davutoglu et al analyzed 40 indoor barbecue workers as models of chronic CO exposure. They found that CO exposure could result in increased thickness of carotid intima-media and serum C-reactive protein level. These effects may increase the risk of cardiovascular events in patients with CO poisoning.<sup>20</sup> Based on the results of these above 2 studies, CO could lead to atherogenic processes either in coronary arteries or in peripheral artery systems. Second, several case reports have shown that acute CO poisoning could result in subsequent arterial thrombosis in the intracardiac region.<sup>21</sup> Furthermore, several studies have also demonstrated hypercoagulable states in patients with CO exposure, a common result of cigarette smoking, leading to enhanced plasmatic hypercoagulation and carboxyhemefibrinogen formation. These factors are critical for the development of atherosclerotic or thrombotic diseases.<sup>22,23</sup> Although these above findings could support CO is a potential atherogenic risk factor, atherosclerosis is a long-term systemic disease and it is hard to completely elucidate the short-term CO exposure with atherosclerosis progression clearly. In previous literatures, when CO enters systemic circulation, it affects vascular endothelial cells by binding to cytochrome oxidase in the mitochondria. The normal electron-transport chain could be broken and

**TABLE 2.** Incidence and Hazard Ratio of Peripheral Arterial Disease Between Patients With Carbon Monoxide Poisoning and Without Carbon Monoxide Poisoning

Outcome	Carbon Monoxide Poisoning						Carbon Monoxide Poisoning to Non-Carbon Monoxide Poisoning	
	Yes			No			Crude HR <sup>†</sup> (95% CI)	Adjusted HR <sup>‡</sup> (95% CI)
	Event	PY	Rate <sup>#</sup>	Event	PY	Rate <sup>#</sup>		
All	25	40,997	6.10	46	178,695	2.57	2.36 (1.45, 3.84) <sup>***</sup>	1.85 (1.12, 3.06) <sup>*</sup>
Sex								
Female	10	20,434	4.89	15	85,857	1.75	2.80 (1.26, 6.23) <sup>*</sup>	2.43 (1.07, 5.53) <sup>*</sup>
Male	15	20,563	7.29	31	92,838	3.34	2.18 (1.17, 4.03) <sup>*</sup>	1.57 (0.82, 2.99)
Age, years								
≤49	12	34,453	3.48	9	146,713	0.61	5.67 (2.39, 13.5) <sup>***</sup>	3.25 (1.28, 8.27) <sup>*</sup>
≥50	13	6544	19.9	37	31,982	11.6	1.71 (0.91, 3.22)	1.10 (0.57, 2.11)
Comorbidity <sup>§</sup>								
No	11	34635	3.18	23	169,655	1.36	2.34 (1.14, 4.80) <sup>*</sup>	3.27 (1.58, 6.78) <sup>**</sup>
Yes	14	6362	22.0	23	9040	25.4	0.86 (0.44, 1.68)	1.20 (0.61, 2.38)

Adjusted HR<sup>‡</sup> = multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, and smoking-related diseases; Comorbidity<sup>§</sup> = patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, heart failure, and smoking-related diseases were classified as the comorbidity group; CI = confidence interval; Crude HR<sup>†</sup> = relative hazard ratio; PY = person-years; Rate<sup>#</sup> = incidence rate per 1000 person-years.

\**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.

interrupted, resulting in anaerobic respiration, the formation of free radicals, and subsequent oxidative stress.<sup>24</sup> In previous animal studies, lower concentrations of CO have been shown to increase oxidative stress, inducing pathological changes in cardiomyocyte.<sup>6,25</sup> This oxidative stress caused by toxicological free radicals results in endothelial cell damage, inflammatory reactions, and subsequent atherogenic processes in peripheral artery circulative systems.<sup>26–28</sup>

HBO therapy has been recommended in patients with CO poisoning presenting with several conditions such as carboxyhemoglobin levels above 25%, evidence of ongoing end-organ ischemia, loss of consciousness, or pregnancy in women.<sup>8,29,30</sup> In Taiwan, HBO therapy is generally applied consistently with the previous recommendations, and in our study, HBO therapy was used as a marker for patients with CO poisoning who presented severe clinical manifestations. Regardless of whether

HBO therapy was administered, the incidence rate for developing PAD among the CO poisoning patients in our study was higher than patients without CO poisoning and the normal control population. This result may be attributable to several factors. First, the number of patients in our study who received HBO therapy was small (*n* = 7). Second, CO poisoning affecting the entire body could irreversibly bind to cytochrome oxidase in the mitochondria. Although the patients in our study received HBO therapy for immediate management of the toxicological effects of CO, these effects could have permanently damaged cells throughout the patients' entire bodies, particularly in the cardiovascular and neurological systems.

In our study, the joint effects analyses revealed that CO poisoning was an independent risk factor for PAD development compared with the normal control population (adjusted HR = 2.95). Furthermore, among the CO poisoning patients

**TABLE 3.** Cox Proportional Hazard Regression Analysis for the Risk of Peripheral Arterial Disease-Associated Carbon Monoxide Poisoning With Joint Effect of Comorbidity, and Hyperbaric Oxygen Therapy

Variables	N	Event n	Adjusted HR <sup>†</sup> (95% CI)
Carbon monoxide poisoning			
No	33,903	23	1 (Reference)
No	2280	23	4.57 (2.36, 8.86) <sup>***</sup>
Yes	7270	11	2.95 (1.43, 6.09) <sup>***</sup>
Yes	1776	14	6.27 (3.10, 12.7) <sup>***</sup>
Carbon monoxide poisoning			
No	36,183	46	1 (Reference)
Yes	6924	18	2.23 (1.29, 3.84) <sup>**</sup>
Yes	2122	7	4.56 (2.05, 10.1) <sup>***</sup>

N indicates the total number of patients in each study group; for example, 34,016 cases did not have comorbidity and CO poisoning.

Adjusted HR<sup>†</sup> = adjusted for age and sex; Comorbidity<sup>§</sup> = patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, heart failure, and smoking-related diseases were classified as the comorbidity group.

\*\**P* < 0.01, \*\*\**P* < 0.001.

**TABLE 4.** Trends of Peripheral Arterial Disease Risks by Stratified Follow-Up Years

Follow-up, Time, years	Carbon Monoxide Poisoning						Crude HR <sup>†</sup> (95% CI)	Adjusted HR <sup>‡</sup> (95% CI)
	Yes			No				
	Event	PY	Rate	Event	PY	Rate		
≤3	14	21,236	6.59	22	91,361	2.41	2.72 (1.39, 5.31)**	1.08 (1.05, 1.10)***
4–6	8	13,128	6.09	14	57,794	2.42	2.52 (1.06, 6.00)*	1.01 (0.98, 1.03)
>6	3	6632	4.52	10	29,541	3.39	1.33 (0.37, 4.84)	1.01 (0.97, 1.05)

Adjusted HR<sup>‡</sup> = hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, heart failure, and smoking-related diseases; CI = confidence interval; Crude HR<sup>†</sup> = relative hazard ratio; PY = person-years; Rate = incidence rate per 1000 person-years.

\**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.

in our study, comorbidities were shown to further increase the risk of PAD compared with control groups (adjusted HR = 6.27). Because the presence of multiple comorbidities in CO poisoning patients increases the risk of PAD development, clinicians should be aware of these comorbidities and identify them as early as possible. In addition, treating these comorbidities in a timely manner is paramount.

Indeed, several limitations existed in our current study. First, the detailed information regarding patients' current use of medications, such as hormone replacement therapy, and previous anticoagulant treatments, which might have influenced the primary study outcomes, were not available in the NHIRD. Second, the health insurance claims database lacked detailed information such as certain critical cardiovascular risk factors, including smoking, obesity, body mass index (BMI), exercise, and dietary habits. Among these missing data, smoking is a relatively crucial risk factor for developing PAD in patients with CO poisoning and the normal control population and is therefore a confounding factor in this study. Consequently, as with previous publications, we adjusted for several comorbidities of smoking-related diseases (including CAD, COPD, asthma, and ischemic stroke) to make the potential confounding effect of smoking on our study results minimally. These adjust models had been utilized in previous studies. In addition, to adjust for the influence of BMI and obesity, we included several traditional metabolic syndrome comorbidities such as hypertension, diabetes, and hyperlipidemia.<sup>31,32</sup> Third, indeed, some asymptomatic patients with PAD existed in our presented study, which may have resulted in the underestimation of PAD in the CO poisoning groups or normal control population in our study. Fourth, certain detailed information regarding patients with CO poisoning, including laboratory results of carboxyhemoglobin and lactate levels, clinical manifestations such as the presence of neurological sequelae, and other factors that may illustrate the chronic complications of CO poisoning were not obtained in the NHRI database. Detailed individual differences should be investigated in additional studies. Fifth, the presented retrospective cohort studies had typically lower statistical quality than evidence derived from large-scale prospective studies. Sixth, in our study, more chronic comorbidities were observed in patients with CO poisoning than control patients, and the cause of PAD in the patients with CO poisoning might have been these comorbidities. However, no evidences in our study could be provided to differentiate the relationship between CO poisoning and PAD from the relationship between comorbidities and PAD. Seventh, our study was only conducted for the general population of Taiwan. Differences may exist between

the population examined in our study and other interethnic, geographical, and epidemiological distributions.

The main strength of this study is a large number of patients with CO intoxication to determine that patients with CO intoxication exhibited a 1.85-fold risk of developing PAD compared with the general population. And there were higher incidence rates for developing subsequent PAD also observed in patients with more chronic comorbidities. Although the detailed pathophysiological mechanism between CO poisoning and PAD may require further examination, PAD is a possible complication in patients with CO poisoning. Future studies might assist physicians in developing strategies to prevent PAD.

**REFERENCES**

- Iqbal S, Clower JH, King M, et al. National carbon monoxide poisoning surveillance framework and recent estimates. *Public Health Rep.* 2012;127:486–496.
- Thom SR, Bhopale VM, Fisher D. Hyperbaric oxygen reduces delayed immune-mediated neuropathology in experimental carbon monoxide toxicity. *Toxicol Appl Pharmacol.* 2006;213:152–159.
- Thom SR, Bhopale VM, Fisher D, et al. Delayed neuropathology after carbon monoxide poisoning is immune-mediated. *Proc Natl Acad Sci U S A.* 2004;101:13660–13665.
- Thom SR, Bhopale VM, Han ST, et al. Intravascular neutrophil activation due to carbon monoxide poisoning. *Am J Respir Crit Care Med.* 2006;174:1239–1248.
- Shen CH, Peng CK, Chou YC, et al. Predicting duration of mechanical ventilation in patients with carbon monoxide poisoning: a retrospective study. *J Crit Care.* 2015;30:19–24.
- André L, Gouzi F, Thireau J, et al. Carbon monoxide exposure enhances arrhythmia after cardiac stress: involvement of oxidative stress. *Basic Res Cardiol.* 2011;106:1235–1246.
- Ruth-Sahd LA, Zulkosky K, Fetter ME. Carbon monoxide poisoning: case studies and review. *Dimens Crit Care Nurs.* 2011;30:303–314.
- Weaver LK. Clinical practice. Carbon monoxide poisoning. *N Engl J Med.* 2009;360:1217–1225.
- Teksam O, Gumus P, Bayrakci B, et al. Acute cardiac effects of carbon monoxide poisoning in children. *Eur J Emerg Med.* 2010;17:192–196.
- Henry CR, Satran D, Lindgren B, et al. Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning. *JAMA.* 2006;295:398–402.
- Lee FY, Chen WK, Lin CL, et al. Carbon monoxide poisoning and subsequent cardiovascular disease risk: a nationwide population-based cohort study. *Medicine.* 2015;94:e624.

12. Lippi G, Rastelli G, Meschi T, et al. Pathophysiology, clinics, diagnosis, and treatment of heart involvement in carbon monoxide poisoning. *Clin Biochem*. 2012;45:1278–1285.
13. Markey MA, Zumwalt RE. Fatal carbon monoxide poisoning after the detonation of explosives in an underground mine: a case report. *Am J Forensic Med Pathol*. 2001;22:387–390.
14. Chen JJ, Lee CH, Lin LY, et al. Determinants of lower extremity amputation or revascularization procedure in patients with peripheral artery diseases: a population-based investigation. *Angiology*. 2011;62:306–309.
15. Chang NT, Chan CL, Lu YT, et al. Invasively-treated incidence of lower extremity peripheral arterial disease and associated factors in Taiwan: 2000–2011 nationwide hospitalized data analysis. *BMC Public Health*. 2013;13:1107.
16. Nelson KM, Reiber G, Kohler T, et al. Peripheral arterial disease in a multiethnic national sample: the role of conventional risk factors and allostatic load. *Ethn Dis*. 2007;17:669–675.
17. Chung WS, Lin CL, Kao CH. Carbon monoxide poisoning and risk of deep vein thrombosis and pulmonary embolism: a nationwide retrospective cohort study. *J Epidemiol Community Health*. 2015;69:557–562.
18. Piantadosi CA. Diagnosis and treatment of carbon monoxide poisoning. *Respir Care Clin N Am*. 1999;5:183–202.
19. Schneiderman G, Goldstick TK. Carbon monoxide-induced arterial wall hypoxia and atherosclerosis. *Atherosclerosis*. 1978;30:1–15.
20. Davutoglu V, Zengin S, Sari I, et al. Chronic carbon monoxide exposure is associated with the increases in carotid intima-media thickness and C-reactive protein level. *Tohoku J Exp Med*. 2009;219:201–206.
21. Ryoo SM, Sohn CH, Kim HJ, et al. Intracardiac thrombus formation induced by carbon monoxide poisoning. *Hum Exp Toxicol*. 2013;32:1193–1196.
22. Nielsen VG, Hafner DT, Steinbrenner EB. Tobacco smoke-induced hypercoagulation in human plasma: role of carbon monoxide. *Blood Coagul Fibrinolysis*. 2013;24:405–410.
23. Leone A, Landini L. Vascular pathology from smoking: look at the microcirculation! *Curr Vasc Pharmacol*. 2013;11:524–530.
24. Akyol S, Erdogan S, Idiz N, et al. The role of reactive oxygen species and oxidative stress in carbon monoxide toxicity: an in-depth analysis. *Redox Rep*. 2014;19:180–189.
25. Thom SR, Ischiropoulos H. Mechanism of oxidative stress from low levels of carbon monoxide. *Res Rep Health Eff Inst*. (80):1997:1–19; discussion 21–7.
26. Brass EP. Intermittent claudication: new targets for drug development. *Drugs*. 2013;73:999–1014.
27. Tousoulis D, Andreou I, Antoniadis C, et al. Role of inflammation and oxidative stress in endothelial progenitor cell function and mobilization: therapeutic implications for cardiovascular diseases. *Atherosclerosis*. 2008;201:236–247.
28. Mallika V, Goswami B, Rajappa M. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. *Angiology*. 2007;58:513–522.
29. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med*. 1998;339:1603–1608.
30. Hampson NB, Dunford RG, Kramer CC, et al. Selection criteria utilized for hyperbaric oxygen treatment of carbon monoxide poisoning. *J Emerg Med*. 1995;13:227–231.
31. Yeh CC, Wang HH, Chou YC, et al. High risk of gastrointestinal hemorrhage in patients with epilepsy: a nationwide cohort study. *Mayo Clin Proc*. 2013;88:1091–1098.
32. Hsu YH, Muo CH, Liu CY, et al. Hepatitis C virus infection increases the risk of developing peripheral arterial disease: a 9-year population-based cohort study. *J Hepatol*. 2015;62:519–525.