The Expert Clinician

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A 53-Year-Old Woman with Severe Carbon Monoxide Poisoning

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Case Vignette

A 60-year-old woman with a medical history of depression, anxiety, and prior suicide attempts presented after being found unconscious in an enclosed garage with the car engine running. Carbon monoxide (CO) levels in the garage were in the range of 120 ppm at the time of her discovery, and the duration of her exposure was unknown.

She required intubation in the field for airway protection. On arrival in the emergency room, her heart rate was 120–130 beats per minute and her blood pressure was 78/57 mm Hg. Her initial arterial blood gas analysis was

notable for a pH of 7.32, P_{CO}₂ of 33 mm Hg, P_O₂ of 380 mm Hg, bicarbonate of 16 mEq/L, and a carboxyhemoglobin level of 24.0%, which decreased to 1.3% after 5 hours of 100% oxygen administration. Due to her initial clinical instability, including her ongoing need for mechanical ventilation, hyperbaric oxygen therapy was not initiated. Labs were notable for lactate 4.5 mmol/L, anion gap of 16, and toxicology screen negative for volatile alcohols, ethanol, acetaminophen, or salicylate. Complete blood count was within normal limits, and urine drug screen was only positive for benzodiazepines. Her initial troponin level was 0.98 ng/ml (normal <0.012 ng/ml), and

her ECG was notable only for sinus tachycardia.

Questions

1. What is the differential diagnosis for this patient's hypotension?
2. What are the most appropriate diagnostic tests to perform in a hypotensive patient with CO poisoning?
3. What is the most appropriate therapy for this patient?

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Clinical Reasoning

CO poisoning presents with a wide spectrum of clinical manifestations, ranging from mild symptoms, including dizziness or headache, to very severe intoxications, which may result in coma, shock, or death (1). The differential diagnosis for hypotension in the setting of severe CO poisoning includes: CO-induced myocardial infarction leading to cardiogenic shock; CO-induced left ventricular dysfunction; Takotsubo syndrome; and concomitant cyanide poisoning, which is most commonly observed in the setting of a house fire. In addition, superimposed disorders, including simultaneous overdose of a hypotension-inducing drug (which may also cause altered mentation), infection with severe sepsis, or shock from profound hypovolemia must be considered. These conditions, and other primary medical disorders, can result in hypotension with altered mental status secondary to cerebral hypoperfusion, and may preclude escape from an enclosed space with high levels of ambient CO.

The patient was given intravenous fluids to treat hypotension, but required transient treatment with parenteral norepinephrine. After volume resuscitation, her blood pressure recovered quickly. The patient's CO exposure was not fire-related, decreasing the likelihood of concomitant

cyanide poisoning. Similarly, an underlying infectious process was unlikely, as she was in a normal state of health before her suicide attempt, and did not have fever or other manifestations of severe infection. Although the patient could have overdosed on a prescription medication or an undetectable recreational substance, the greatest concern was for a cardiogenic cause in the setting of elevated serum troponin levels. Thus, we performed a transthoracic echocardiogram, which demonstrated a nondilated left ventricle (LV) with an ejection fraction of 40%. The apex, mid-, and distal anterior septum were akinetic, as was the midposterior wall; these findings were consistent with Takotsubo syndrome without evidence of left ventricular outflow tract obstruction (Figures 1A and 1B, and *see video* in the online supplement). Metoprolol was started on Hospital Day 2, to mitigate the presumed catecholamine surge associated with this disorder. Troponin level decreased to 0.71 ng/ml, and repeat ECG showed lateral T wave inversions.

Discussion

CO binds with high affinity to all ferrous heme-containing proteins, including hemoglobin, myoglobin, and mitochondrial

cytochrome c oxidase (1). CO directly binds to hemoglobin, both reducing binding sites for oxygen and stabilizing the R state of hemoglobin, which impairs oxygen release. These combined effects can dramatically reduce oxygen delivery. In addition, CO inhibition of mitochondrial respiration at complex IV, inhibiting oxidative phosphorylation, reducing cellular oxygen utilization, and generating reactive oxygen species, all of which likely account for the cardiotoxic effects of CO poisoning (1, 2).

CO poisoning can cause long-term neurocognitive deficits, a potentially devastating injury estimated to impact up to 40% of survivors (1). There is no antidotal therapy for CO poisoning, although drugs are being researched (3, 4); treatment options include normobaric and hyperbaric oxygen therapy. There have been several randomized clinical trials comparing hyperbaric with normobaric oxygen therapy (5). The most widely referenced and best designed of these trials suggested a reduction in long-term neurocognitive deficits; however, a meta-analysis did not endorse the efficacy of hyperbaric oxygen therapy in reducing neurocognitive injury (5–7). Regardless, hyperbaric oxygen therapy has logistical limitations, as it is available in approximately 250 centers nationwide, which can lead to significant treatment delays (1).

Up to one-third of patients with moderate or severe CO poisoning have been reported to demonstrate some degree of myocardial injury, and those who survive appear to have an increased risk of mortality going forward (8). The inhibition of oxidative phosphorylation, and the direct binding of CO to myoglobin (which has a 60-fold greater affinity for CO than oxygen), can cause myocardial infarction and cardiac dysfunction even in the absence of underlying coronary disease (9). The effects of CO on mitochondrial respiration could potentially cause a myocardial stunning (9). With the inhibition of oxidative phosphorylation, ATP availability is decreased and calcium gradients are altered, leading to increased calcium sensitivity of myofilaments and increased diastolic intracellular calcium (9). These factors, combined with the physical stress of the global hypoxic state from CO, lead to a hyperadrenergic state, resulting in a variety of arrhythmias and, in a small but significant number of cases, CO-induced Takotsubo syndrome (9, 10).

Figure 1. Echocardiography demonstrates apical ballooning. (A and B) Apical four-chamber view of echocardiography demonstrated a nondilated left ventricle (LV) with an ejection fraction of 40% with an akinetic apex, mid-, and distal anterior septum and midposterior wall, consistent with Takotsubo syndrome. (C and D) Follow-up echocardiography demonstrated normal LV function with an ejection fraction of 55–60% on apical four-chamber view, and *see video* in the online supplement.

Two representative studies outline the magnitude of this clinical problem. In one study of 132 CO-poisoned patients, 29 (22%) demonstrated LV dysfunction on echocardiography, and of these, 8 (6%) had apical ballooning consistent with Takotsubo syndrome (10). In a separate study, focusing only on CO-poisoned patients with high troponin levels, the incidence of a Takotsubo-like pattern was 23% (11). Although CO poisoning is associated with multiple types of LV dysfunction, there does appear to be some correlation between severity of CO poisoning and the pattern of ventricular dysfunction (10).

Takotsubo syndrome is defined by reversible LV dysfunction after a period of acute, severe stress. Diagnosis is established if patients fulfill all four Modified Mayo Criteria (Table 1) (12). Due to its association with emotional or physical stress (such as cocaine use or subarachnoid hemorrhage), the pathogenesis of Takotsubo syndrome is believed to be mediated by catecholamine-induced microvascular spasm and/or direct catecholamine-associated myocardial toxicity (13–15). Calcium overload in cardiomyocytes from catecholamine excess and the direct effects of catecholamines trigger a switch from stimulatory G protein activation to inhibitory pathways through β_2 -adrenergic receptors, ultimately leading to hypocontractility in cardiomyocytes and ventricular dysfunction (10, 16). Increased apical sensitivity to catecholamines has been suggested as the causal mechanism for the typical apical ballooning noted in this disorder (10). In addition to the “standard” catecholamine-mediated pathogenesis of Takotsubo syndrome,

patients with CO poisoning may also experience direct effects, including coronary vasoconstriction, decreased global oxygen delivery, and CO binding to cytochrome c oxidase or myoglobin, all of which can contribute to myocardial stunning (8, 9).

Up to 20% of patients with Takotsubo syndrome develop cardiogenic shock, either from severe LV systolic dysfunction or from LV outflow tract obstruction (17). Without significant pulmonary congestion, intravenous fluids may be given with caution to increase LV preload. Inotropic and vasopressor support can be used as temporizing measures in this setting; however, there is concern that inotropes may exacerbate the catecholamine surge and result in clinical deterioration (17–19). In addition, inotropes can cause LV outflow tract obstruction in Takotsubo syndrome (18). In cases of Takotsubo syndrome with LV outflow tract obstruction, inotropic agents are absolutely contraindicated as they may worsen the degree of obstruction (18, 19). These patients should be treated in a manner similar to those with hypertrophic cardiomyopathy, where β blockers may help reduce the obstruction and lead to resolution of shock (17, 19). If available, mechanical support (LV assist devices or extracorporeal membrane oxygenation) is recommended over inotropic therapy to support perfusion in Takotsubo syndrome with acute cardiogenic shock, to avoid worsening the injury caused by catecholamine surge (17, 19). Intra-aortic balloon counterpulsation may be an option in the absence of LV outflow tract obstruction; however, it can worsen dynamic obstruction, and should not be used if present (17, 19).

Table 1. Modified Mayo criteria for the diagnosis of Takotsubo cardiomyopathy

1. Transient hypokinesis, akinesis, or dyskinesis in the left ventricular midsegments, with or without apical involvement; regional wall motion abnormalities beyond single vascular territory in the presence of a stress trigger.
2. Absence of coronary disease or angiographic evidence of plaque rupture
3. New electrocardiographic abnormalities or modest elevation of cardiac troponin
4. Absence of pheochromocytoma or myocarditis

Answers

1. What is the differential diagnosis for this patient's hypotension?

CO-induced myocardial infarction, leading to cardiogenic shock, CO-induced left ventricular dysfunction in the absence of infarction, or Takotsubo syndrome. Other noncardiogenic causes, including septic shock, hypovolemic shock, or medication coingestion, are possible, but much less likely.

2. What are the most appropriate diagnostic tests to perform in a hypotensive patient with CO poisoning?

While excluding cyanide exposure, infectious etiologies, hypovolemia, or concomitant drug overdose, immediate evaluation of cardiovascular performance with ECG, troponin levels, and transthoracic echocardiography is recommended.

3. What is the most appropriate therapy for this patient?

Patients with Takotsubo syndrome and hypotension should be managed first with cautious fluid resuscitation; in those in cardiogenic shock with end-organ dysfunction, mechanical support is favored over inotropes, to avoid worsening the catecholamine surge and/or LV outflow tract obstruction.

Follow-Up

Though she suffered a significant anoxic brain injury, the patient demonstrated gradual improvement, was extubated, and was eventually discharged to inpatient rehabilitation. Subsequent transthoracic echocardiogram demonstrated complete recovery of left ventricular function (Figures 1C and 1D).

Insights

- The differential diagnosis for hypotension in the setting of CO poisoning requires consideration of the mechanism of exposure (particularly the presence or absence of fire), possible concomitant ingestions, and underlying medical illnesses.
- Cardiovascular dysfunction in moderate or severe CO poisoning is quite common, and can result from several mechanisms alone or in combination.
- Takotsubo syndrome should be considered early in the evaluation of patients with hypotension after CO exposure. Inotropes should be avoided in confirmed cases of Takotsubo syndrome, and are absolutely contraindicated in patients with LV outflow tract obstruction. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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