JACC: HEART FAILURE VOL. ■, NO. ■, 2024

PUBLISHED BY ELSEVIER

REVIEW TOPIC OF THE MONTH

Practical Recommendations for the Evaluation and Management of Cardiac Injury Due to Carbon Monoxide Poisoning

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HIGHLIGHTS

- Cardiotoxicity following CO poisoning is an underrecognized problem with severe long-term risks.
- Patients with CO poisoning should be immediately screened for signs of cardiac impairment.
- This review provides a flow diagram for the short- and long-term evaluations of such patients.
- Specific treatment options for patients with CO poisoning need to be evaluated in future studies.

ABSTRACT

Carbon monoxide (CO) is a relatively frequent cause of poisoning evaluated in emergency departments. The risk of neurologic injuries, such as cognitive, psychological, vestibular, and motor deficits, is 25% to 50%. However, the risk of cardiac injuries should also be considered. Among patients with CO poisoning, the mortality in patients with myocardial injury is approximately 3 times greater than that in patients without myocardial injury. In large-scale studies, up to 69.2% of patients with acute CO poisoning exhibiting elevated troponin I levels and no underlying cardiovascular illnesses had late gadolinium enhancement on cardiac magnetic resonance, suggesting covert CO-induced myocardial fibrosis. Myocardial damage can be evaluated using electrocardiography, echocardiography, computed tomography, and cardiac magnetic resonance. This paper offers recommendations for cardiac evaluations based on our collective experience of managing >2,000 cases of acute CO poisoning with supporting information taken from peer-reviewed published reports on CO poisoning. (J Am Coll Cardiol HF 2024;■:■–■) © 2024 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received December 1, 2023; revised manuscript received January 2, 2024, accepted January 3, 2024.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2024.01.001

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CMR = cardiac magnetic resonance

CO = carbon monoxide

COHb = carboxyhemoglobin

CTA = computed tomography angiography

ECG = electrocardiogram

ED = emergency department

HBO_2 = hyperbaric oxygen therapy

LGE = late gadolinium enhancement

TnI = troponin I

TTE = transthoracic echocardiography

Approximately 50,000 individuals with carbon monoxide (CO) poisoning are admitted to hospital emergency departments (EDs) in the United States each year.[1] CO is a common, potentially lethal gas produced by the incomplete combustion of fossil fuels, such as natural or liquefied petroleum gas, oil, wood, and coal. Gasoline-powered generators, charcoal grills and briquettes, kerosene heaters, and stoves are the main household sources of unintentional CO poisoning.[2] Between 2015 and 2021, on average, 1,167 annual deaths from CO poisoning were reported.[1] Despite the declining number of CO-related deaths from 1,253 in 2015 to 1,067 in 2021, accidental CO deaths in the United States exceeded the number of intentional CO deaths for the first time in 2021.[1] The decline in CO-related mortality has been ascribed to a reduction in CO emissions from automobiles and possibly to prevention efforts and improved treatment methods.[3] In addition, the use of CO from automobiles as a suicide method has been discouraged by the introduction of catalytic converters and more stringent automobile emission standards.[1]

The most well-recognized risk of CO poisoning is neurocognitive sequelae.[4] The annual societal expenses of accidental CO poisoning in the United States (hospital bills and missed wages) are estimated to exceed $1.3 billion.[1] The U.S. Centers for Disease Control and Prevention has publicized a *Carbon Monoxide Poisoning Fact Sheet* in which they recommend the following steps to keep families safe from CO: install battery-operated or battery-backup CO detectors near every sleeping area; have oil/gas furnaces inspected annually; and use portable gas-operated generators >20 feet away from homes, and never operate them inside the home or garage.[5]

IMPORTANCE OF THE EVALUATION OF CARDIAC INJURY FOLLOWING CO POISONING

Even low levels of carboxyhemoglobin (COHb) can cause myocardial ischemia during graded exercise in individuals with coronary artery disease,[6] and small amounts of CO inhaled by people with stable angina pectoris can lower their pain threshold.[7] CO poisoning can also cause cardiac injuries.[8-11] In a previous study, 20% of patients with acute CO poisoning experienced myocardial damage with elevated levels of troponin I (TnI), a biomarker reflecting the burden of myocardial injury.[9] In a follow-up study with echocardiography,[10] 74.4% of CO-poisoned individuals with high TnI levels had CO-related myocardial injury, including global myocardial dysfunction and takotsubo cardiomyopathy, although these abnormalities normalized in many cases. Notably, TnI levels returned to normal within a median of 65 hours,[9] and echocardiography revealed that global myocardial dysfunction also largely resolved.[10] These observations led clinicians to believe that myocardial injury is common but without clinical importance in patients with CO poisoning. However, in a long-term follow-up study,[12] the mortality of CO-poisoned patients who sustained myocardial injury was 3 times that of patients without myocardial injury. Data from a nationwide cohort study revealed higher incidence rates of serious adverse cardiovascular events in the months following CO poisoning.[13-15]

How can we explain the short-term normalization of test findings while observing an increase in long-term mortality? To address this question, we conducted a cardiac magnetic resonance (CMR) study during the acute phase of CO poisoning and at 3 to 6 months of follow-up to observe the pattern of myocardial damage.[11] In 69.2% of patients with acute CO poisoning, increased TnI levels, and no underlying cardiovascular illnesses, CMR showed late gadolinium enhancement (LGE). LGE, a noninvasive approach, is suggestive of myocardial fibrosis, which is associated with adverse cardiac events.[16] At 4 months of follow-up, CMR indicated no change in LGE (67.6%) or LGE worsening (5.4%) in these patients.[11] In an animal study, CO poisoning also caused remarkable myocardial fibrotic injury.[15] These findings suggest that long-term fibrotic damage to the myocardium may occur in acute CO poisoning.

DIFFICULTY OF EVALUATION OF CARDIAC INJURY

Diagnosing cardiac injury and dysfunction in patients with CO poisoning can be challenging because of the lack of specific clinical signs and symptoms, as well as the unreliability of electrocardiogram (ECG) and cardiac biomarker changes to reflect the degree of injury and impairment. CO exposure may also be underrecognized as a cardiac risk factor because evidence-based practical recommendations for evaluating cardiac injury following CO poisoning are not established.[17] Therefore, we propose clinical recommendations for the short- and long-term evaluation of cardiac injuries in patients with CO poisoning.

PATHOGENESIS OF CO-INDUCED CARDIAC INJURY

The possible mechanisms for cardiac damage following CO poisoning are shown in the **Central Illustration**.

DIRECT MYOCARDIAL DAMAGE. The affinity of CO to the heme group of myoglobin in cardiomyocytes is 60-fold higher than that of oxygen. Of CO-poisoned patients with LGE-positive CMR, most exhibited midwall injuries, whereas subendocardial injuries were relatively rare.[11] This suggests that the primary mechanism causing myocardial damage in CO poisoning may not be myocardial ischemia but, rather, direct CO cardiotoxicity because myocardial ischemia would typically manifest as a subendocardial LGE pattern.[11]

HYPOXIA. CO binds to hemoglobin with a much greater affinity than oxygen, resulting in hypoxemia of tissues, including the myocardium.[18] Increased cardiac output and oxygen extraction occur to compensate for the reduced systemic oxygen delivery attributable to COHb.[18] This may lead to high-output heart failure and consequent death when compensatory systems are overwhelmed.[18,19]

INHIBITION OF MITOCHONDRIA. Especially with concomitant hypoxia, CO can bind to mitochondrial cytochromes, lowering mitochondrial respiration and inhibiting oxidative phosphorylation, thus reducing the heart's ability to produce adenosine triphosphate.[4,19,20] CO-induced myocardial injury in patients with underlying coronary artery disease is well recognized,[21] but CO can even cause myocardial stunning and injury in the absence of obstructed coronary arteries.[22,23]

THROMBUS FORMATION. High CO levels can cause intravascular thrombosis, perhaps caused by CO binding to fibrinogen-bound heme and enhanced platelet aggregation.[21] CO, possibly in settings with multiple air contaminants, may increase the incidence of arterial and venous thrombosis.[22] However, as stated, clinical findings in patients with CO poisoning indicate that these events are rare.[11,24] This is also supported by a previous study that demonstrated no evidence of CO-induced coronary artery stenosis, and coronary computed tomography angiography (CTA) showed no differences in coronary artery stenosis according to the presence or absence of CO-related myocardial injury.[24]

OXIDATIVE STRESS. CO promotes the expression of inducible nitric oxide synthase during ischemia reperfusion, which causes nitric oxide-induced myocardial injury.[25] Additionally, CO poisoning activates platelets, which, once bound to neutrophils, trigger their degranulation and perivascular myeloperoxidase deposition. This can amplify inflammatory processes via progressive neutrophil activation, adhesion, and degranulation.[19,26] Thus, CO-induced cardiac damage can be caused by inflammatory responses and associated increases in reactive oxygen species levels.[19]

ARRHYTHMIAS. The threshold for malignant ventricular arrhythmias is decreased by CO exposure, and even very low amounts of COHb can decrease the myocardial threshold for ventricular fibrillation.[23,27] Arrhythmias and other pathologic ECG patterns are frequently caused by CO.[28-30] They may arise because of the hyperadrenergic state prompted by the aforementioned mechanisms or because of coronary vasoconstriction caused by global endothelial dysfunction.[22]

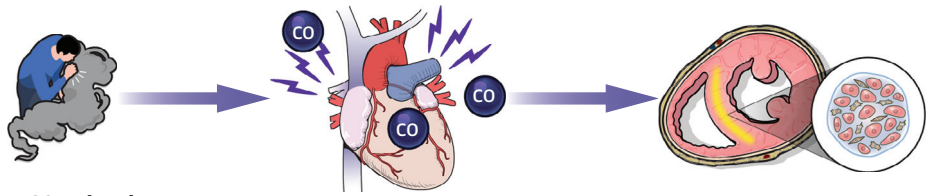
The CO-induced enhanced intracellular NO availability can also increase the late component of inward sodium currents, alter Ca^{2+} gradients, and increase the Ca^{2+} sensitivity of myofilaments.[31,32]

APPROACHES FOR ASSESSING CO-INDUCED MYOCARDIAL INJURY

CO-induced myocardial injury can even occur in the absence of cardiac symptoms.[33] Therefore, patients with suspected CO exposure should be evaluated for myocardial injury.[34] The following ancillary tests should be considered during initial and follow-up evaluations: 1) ECG; 2) cardiac enzymes (TnI); 3) B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide (NT-proBNP); 4) transthoracic echocardiography (TTE); 5) coronary CTA; and 6) CMR.

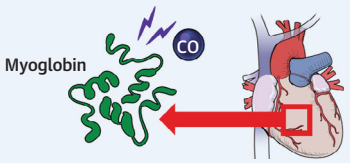
ELECTROCARDIOGRAPHY. ECG is a screening tool for diagnosing the presence of CO-induced cardiac injury. In 250 patients with CO poisoning, the initial ECGs showed sinus tachycardia (15.2%), ischemic ECG abnormalities (3.6%), and normal sinus rhythm (54.4%).[9] Other reported ECG patterns were supraventricular arrhythmias, such as sinus tachycardia, atrial fibrillation, premature atrial complexes, or wandering pacemaker, and ventricular arrhythmias, including premature ventricular complexes.[29,35] CO poisoning can unmask familial Brugada syndrome and occult coronary artery disease,[28,36] and it can cause variant angina and myocardial ischemia, even among those with limited or no coronary atherosclerosis.[27] Although relatively uncommon, case reports

CENTRAL ILLUSTRATION **Pathophysiology and Management of Cardiac Injuries From Carbon Monoxide Poisoning**



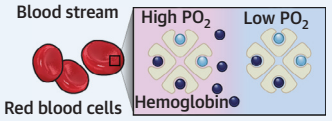
CO Cardiac Injury

1. Direct myocardial toxicity



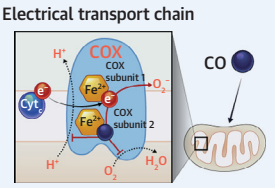
- ↑ Affinity for the myoglobin

2. Hypoxia



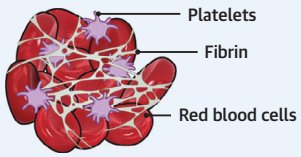
- ↑ Affinity for hemoglobin
- Stabilization of Hb to oxygen

3. Mitochondrial inhibition



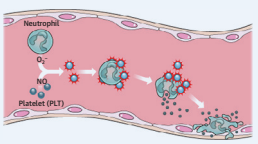
- CO-induced direct inhibition of mitochondria→ ↓ ATP production

4. Thrombus formation



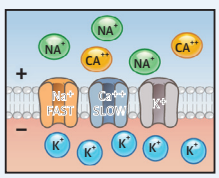
- CO binding to fibrinogen
- ↑ Platelet aggregation

5. Oxidative stress



- CO → ↑ INOS → NO-induced damage
- CO → ↑ Platelet and neutrophil activation

6. Arrhythmia risk ↑



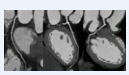
- Modulation of Na^+ channels
- Alteration of Ca^{2+} gradients

Evaluation for CO-Induced Cardiac Injury

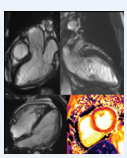
- Electrocardiogram

- Troponin I

- Echocardiography



- Coronary computed tomography angiography



- Cardiac magnetic resonance image

Follow-up (cardiology OPD)

Cho D-H, et al. J Am Coll Cardiol HF. 2024;■(■):■-■.

ATP = adenosine triphosphate; Ca = calcium; CO = carbon monoxide; COX = cytochrome c oxidase; Hb = hemoglobin; INOS = inducible nitric oxide synthase; K = potassium; Na = sodium; O_2 = oxygen; NO = nitric oxide; OPD = outpatient department; PO_2 = partial pressure of oxygen.

of both non-ST-segment elevation[36] and ST-segment elevation[21,37,38] myocardial infarction exist.

Therefore, it is crucial to initially screen all patients with CO poisoning for ischemic ST-segment changes and QT interval prolongation (an indirect indicator of ventricular repolarization heterogeneity that may predispose to ventricular arrhythmias) and to monitor newly developed ECG abnormalities for 3 to 7 days until normalization.

CARDIAC BIOMARKERS. Serum TnI is helpful for prompt diagnosis of myocardial injury and may guide the treatment of acute CO poisoning.[39] Elevated TnI concentrations were found in 17% to 37% of patients with CO poisoning.[8,9,40] Elevated TnI levels were observed at ED presentation in 72.1% of cases and after admission in 27.9% of cases.[9] The elevated TnI levels peaked at 11.0 hours and returned to normal values at 65.0 hours. Therefore, measurement of TnI repeatedly for 6 to 12 hours following the initial measurement may be beneficial. If follow-up TnI measurements show an upward trend, additional TnI tests should be considered even if the values are within the normal range because the time to peak may vary.[9]

Natriuretic peptides including BNP and NT-proBNP, a class of endogenous mediators, are produced in response to hemodynamic overload–induced myocardial stretch. Both BNP and NT-proBNP might be substitute biomarkers for cardiotoxicity and cardiac dysfunction in CO poisoning.[40,41] In patients with acute CO poisoning, median BNP values were greater in the group with CO-related myocardial injury compared with those in the group with no myocardial injury,[10] and an association was identified between elevated NT-proBNP levels and CO poisoning.[41] Thus, BNP or NT-proBNP might be used as an early indicator of cardiotoxicity in CO poisoning. To prevent overlooking CO-related myocardial injury, regular BNP testing is necessary, especially when echocardiography is unavailable. However, TTE is advisable as a follow-up step to identify CO-related myocardial injury in patients with elevated BNP or TnI levels.[10]

TRANSTHORACIC ECHOCARDIOGRAPHY. In 43 consecutive CO-poisoned patients with myocardial injury identified by elevated TnI levels, TTE in the ED identified CO-related myocardial injury in 74.4% (n = 32).[10] The predominant patterns were global dysfunction (51.2%) and takotsubo cardiomyopathy (23.2%). Normalized TTE within 72 hours was substantially more likely in patients with global dysfunction (81.8%) compared with that in those with takotsubo cardiomyopathy (22.2%). A TTE immediately upon arrival in the ED rather than an elective TTE at a later timepoint is highly likely to detect myocardial dysfunction. Therefore, a bedside TTE or focused cardiac ultrasound in the ED by skilled emergency physicians or cardiologists is advisable. The TTE evaluation should focus on the following 4 factors: 1) the presence or absence of CO-related myocardial injury; 2) whether a potential CO-related myocardial injury corresponds to the territory of a coronary artery; 3) whether an intracardiac thrombus complicates a potential CO-related myocardial injury;[42] and 4) whether left ventricular dysfunction is severe enough to cause shock.[10] All patients with CO poisoning should undergo TTE because CO-related myocardial injury can occur regardless of increased cardiac markers.[10,40]

CORONARY CTA. Because coronary artery stenosis is not the primary mechanism causing CO-related myocardial injury, evaluation of coronary arteries in all patients with CO-related myocardial injury is unnecessary. However, we suggest urgent coronary angiography if a patient's ECG shows signs of ST-segment elevation myocardial infarction consistent with regional wall motion anomalies in TTE. Coronary CTA should also be considered in cases where TTE abnormalities have uncertain associations with coronary artery regions, especially when TTE abnormalities suggest lesions of the left main or anterior descending artery.[24]

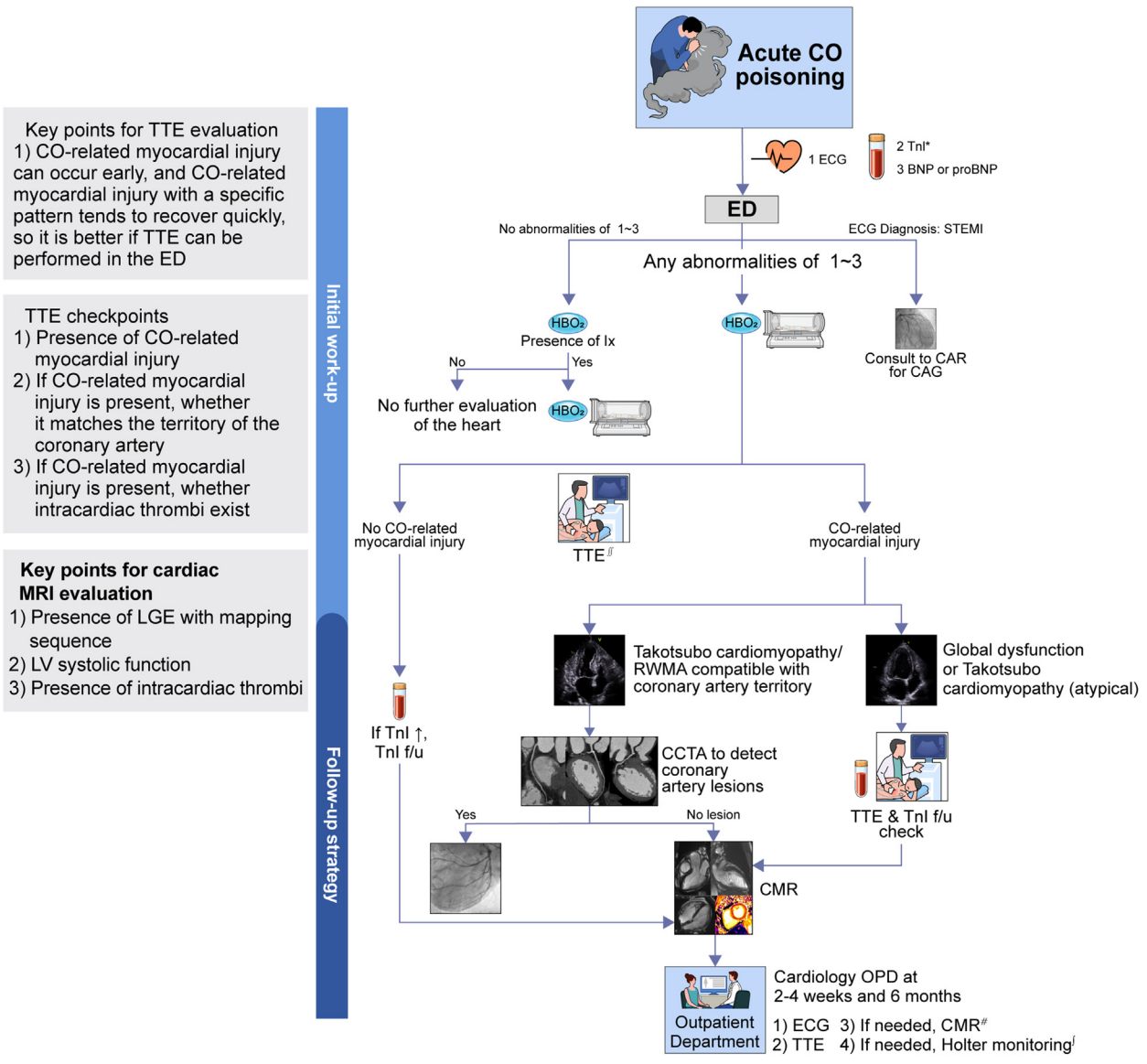
CARDIAC MAGNETIC RESONANCE. CMR commonly identifies LGE in the myocardia of patients (69.2%) with acute CO poisoning and elevated TnI levels.[11] The most common pattern (39.4%) is midwall damage, which is of particular interest because the degree of midwall LGE is an independent risk factor for mortality in patients with nonischemic dilated cardiomyopathy, regardless of left ventricular function.[43] Notably, TTE in the ED identified CO-related myocardial injury in only 42.2% of patients,[11] suggesting that echocardiography may offer false reassurance. Thus, CMR may be advisable in patients with increased TnI levels, regardless of the existence of CO-related myocardial injury. CMR may also be included in follow-up evaluations of patients with myocardial injury.[44]

PRACTICAL STRATEGY FOR THE EVALUATION OF CARDIAC INJURY

Our proposed approach to evaluate cardiac injury in acute CO poisoning is shown in **Figures 1 and 2**.

INITIAL WORK-UP. Clinicians in the ED should check patients with CO poisoning for cardiac injury using ECG, TnI, BNP/NT-proBNP, and TTE. The existence of CO-related myocardial injury can be evaluated using

FIGURE 1 Approach to Evaluate Cardiac Injury in CO Poisoning

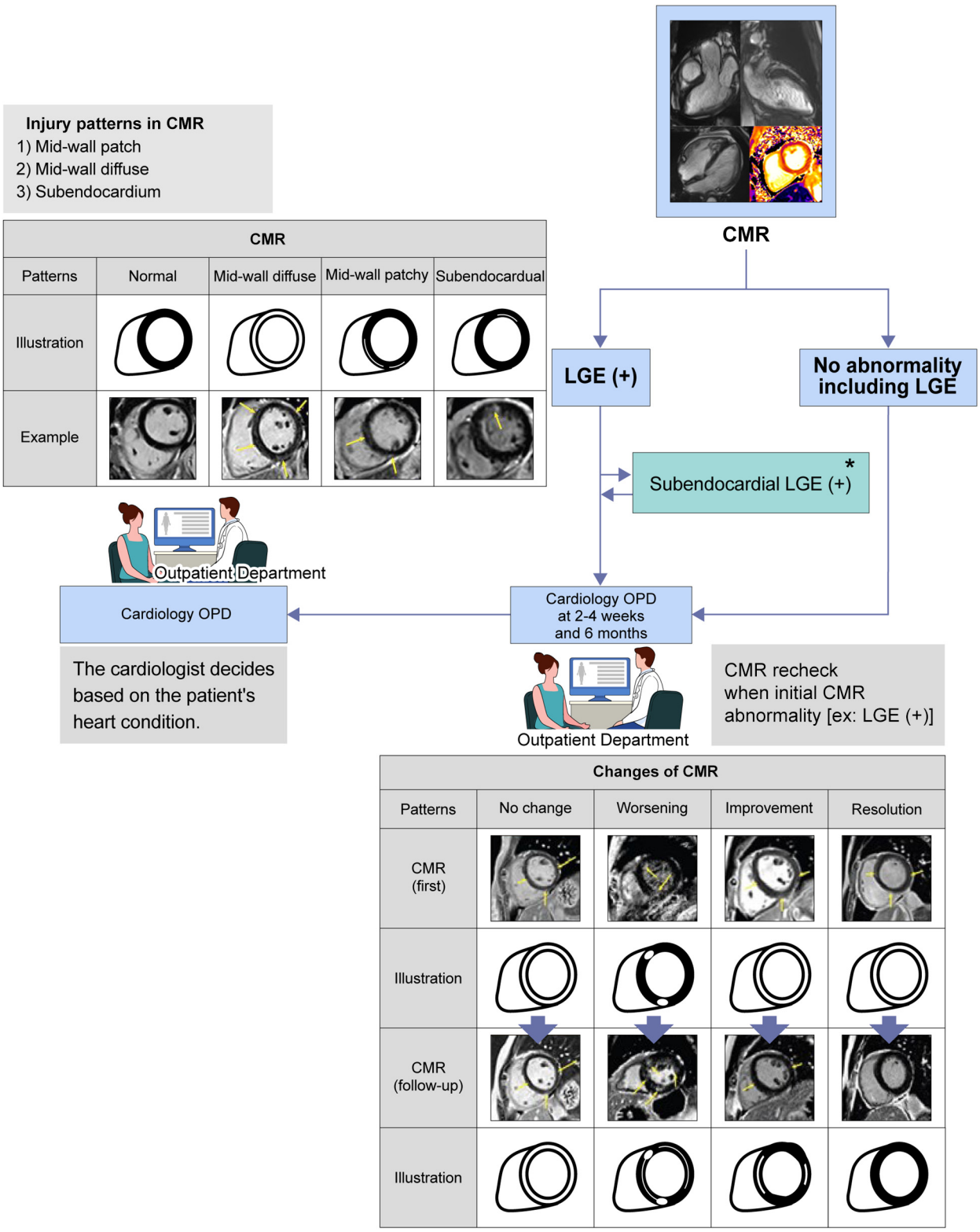


*Follow-up (f/u) at 6-12 h after ED arrival. ‡By emergency physicians at the ED (focused ultrasound). #When initial CMR abnormality (eg, LGE[+]). †When arrhythmia at f/u ECG. BNP = B-type natriuretic peptide; CAG = coronary artery angiography; CAR = cardiology; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; CO = carbon monoxide; ECG = electrocardiography; ED = emergency department; ex = example; f/u = follow-up; HBO_2 = hyperbaric oxygen therapy; Ix = indication; LGE = late gadolinium enhancement; LV = left ventricle; OPD = outpatient department; RWMA = regional wall motion abnormality; STEMI = ST-segment elevation myocardial infarction; TnI = troponin I; TTE = transthoracic echocardiography; Tx = treatment.

TTE or focused cardiac ultrasound (**Figure 1**, Videos 1 and 2). A cardiologist should be consulted for immediate coronary artery angiography if an ECG shows signs of ST-segment elevation myocardial infarction and for possible further interventions with reperfusion therapy or other treatments of coronary artery stenosis.[21,38] CO-induced cardiac injury may be suspected in the presence of other ECG abnormalities, elevated TnI levels, or abnormal echocardiographic findings. TTE can be performed before or after hyperbaric oxygen therapy (HBO_2) depending on facility resources.

FOLLOW-UP STRATEGY. If TTE identifies CO-related myocardial injury, TTE should be serially conducted to assess recovery of myocardial dysfunction. If shock occurs, clinicians should consider the likelihood of a

FIGURE 2 **Evaluation Methods for CO-Induced Cardiomyopathy According to the Specific CMR Findings**



*If an evaluation of the coronary artery has not been previously performed, CCTA or CAG for evaluating masking significant CAD. Abbreviations as in Figure 1.

cardiac cause and, if necessary, administer appropriate medical treatment and strict hemodynamic monitoring. As intracardiac thrombus formation may occur, cerebral infarction and pulmonary thromboembolism should always be considered. If a thrombus is observed, intravenous heparin administration should be considered. Patients with takotsubo cardiomyopathy often require inotropic support and have a higher risk of cerebral infarction and pulmonary thromboembolism.[10]

Coronary CTA can rule out coronary artery lesions in patients with typical takotsubo cardiomyopathy or cardiomyopathy for whom TTE abnormalities overlap with a coronary artery region. In patients with increased TnI levels, CMR should be considered even in the absence of CO-related myocardial injury because these patients are associated with LGE positivity.[11,44] CMR evaluation should focus on the following areas: 1) presence of LGE with a mapping sequence; 2) left ventricular systolic function; and 3) presence of intracardiac thrombi.

If the LGE pattern on CMR suggests subendocardial injury and the patient has no history of coronary artery disease and coronary artery assessment, hypoxia-induced damage may be the primary mechanism causing the injury. Assessing the likelihood of coronary artery stenosis and developing a treatment strategy based on the coronary artery status is necessary in these patients (**Figure 2**). These patients may benefit considerably from standard medical management strategies (antiplatelet and lipid-lowering agents, beta-blockers)[44] of coronary artery disease and, in some cases, coronary angiography with consideration for revascularization, where CO poisoning may have masked an underlying considerable coronary artery disease.[8]

Patients should return for cardiac follow-up reevaluation at 2 to 4 weeks and 6 months after poisoning. To screen for various types of cardiomyopathy and conduction abnormalities, Holter tests are suggested if arrhythmias are detected, and the cardiologist may perform an ECG, TTE, or CMR. The risk of congestive heart failure has been shown to increase with the peak in the first month post-CO poisoning and persist in some patients for more than 2 years.[15]

MANAGEMENT OF CARDIAC INJURY

Studies on the effectiveness of HBO_2 for preventing or treating CO-induced myocardial damage do not exist. However, patients with cardiac injuries should receive HBO_2 given their risk of neurologic sequelae.[45] If any abnormalities in the initial work-up are present or if coronary angiography demonstrates vasospasms or no substantial coronary artery lesions, HBO_2 treatment may prevent central nervous system injury while continuing ECG monitoring. If further indications for HBO_2 exist, HBO_2 should be carried out even if the earlier mentioned tests for cardiac injury reveal no abnormalities.

For patients with CO-induced myocardial dysfunction, specific cardiovascular drug treatments have not been established. When the left ventricular ejection fraction drops to ≤40%, we advise following the general treatment principles for heart failure with reduced ejection fraction and consider the use of the 4 pillars: angiotensin-converting enzyme inhibitors, angiotensin (II) receptor blockers, angiotensin receptor neprilysin inhibitors, and sodium glucose co-transporter 2 inhibitors.[46] One of the leading pathophysiologic causes of heart failure with preserved ejection fraction is myocardial fibrosis, and myocardial fibrotic load is substantially and independently associated with worse outcomes.[47] Pirfenidone, a well-tolerated, small-molecule antifibrotic agent with demonstrated clinical effectiveness and safety in patients with idiopathic pulmonary fibrosis, reduced myocardial fibrosis in patients with heart failure with preserved ejection fraction.[47] However, whether pirfenidone or other options such as implantable defibrillators are beneficial for CO-induced myocardial fibrosis remains unknown.

SPECIAL CONSIDERATIONS

PEDIATRIC PATIENTS. Children (aged <17 years) with CO poisoning can sustain cardiac injuries. In one study, 15% of patients had diagnoses of severe myocardial damage, and low ejection fraction with poor left ventricular function were confirmed by TTE in 33% of patients.[48] Cardiac injury is assessed similarly in children and adults. Additionally, as with adults, HBO_2 is safe for children and should be considered for children with cardiac injuries to lower the risk of brain injuries.[49]

PREGNANCY. Reports of maternal or fetal cardiac damage caused by CO poisoning have not been published. The steady-state level of COHb in pregnant women exposed to CO is typically 10% to 15% lower than that of the fetus because of the CO affinity of hemoglobin F, rendering the developing fetus highly vulnerable to harmful CO effects. Compared with adult blood, fetal blood also requires more time to remove CO, and maternal poisoning and hypoxia exacerbate fetal hypoxia.[20,50] In severe CO poisoning, fetal mortality approaches 50%.[1,50] Cardiac injury is assessed similarly in pregnant and nonpregnant women. HBO_2 use during pregnancy has not been associated with

any adverse neonatal outcomes, and at least one case report describes a favorable outcome with HBO_2.[50] Therefore, treatment is the same for pregnant and nonpregnant women following CO exposure.

CONCLUSIONS

Recent advances in imaging modalities have revealed that myocardial injury is more common in patients with CO poisoning than previously thought, and this finding has implications for long-term mortality. Therefore, myocardial injury should be the foremost consideration in such patients, and early assessment and continuous monitoring are crucial (**Central Illustration**). In this review, we presented a systematic evaluation tool for cardiac injury and a process for follow-up. Additional research on the treatment and prevention of cardiac injury is necessary.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported in part by the National Research Foundation of Korea, which is funded by the Korean government (Ministry of Science and Information and Communications Technology, grant number NRF-2021R1A2C200492211) and by a grant from the National Institutes of Health (National Institute of Neurological Disorders and Stroke) (R01-NS122855). The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS carbon monoxide, cardiac imaging, cardiomyopathies, poisoning

APPENDIX For supplemental videos, please see the online version of this paper.