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Carbon Monoxide-Induced Cardiomyopathy

– Epidemiology, Clinical Characteristics and Prognosis –

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Background: Previous reports demonstrated mechanisms of cardiac toxicity in acute carbon monoxide (CO) poisoning. Still, none established CO-induced cardiomyopathy (CMP) as a clinical entity. The aim of this study is to investigate CO-induced CMP in patients with acute CO poisoning in terms of its epidemiology, clinical characteristics, and prognosis.

Methods and Results: A retrospective study was conducted on consecutive patients who were diagnosed with acute CO poisoning at the emergency department of Ajou University Hospital during the period of 62 month. Six hundred and twenty-six patients were diagnosed with acute CO poisoning. During the initial echocardiography, 19 patients were abnormal: (1) global hypokinesia/akinesia (n=7), (2) regional wall hypokinesia/akinesia [n=12; takotsubo type (n=6), reverse takotsubo type (n=2), non-specific type (n=4)]. The ejection fraction (EF) was 36.3±13.5% (from 15% to 55%) and less than 45% for 14 patients. In the follow-up echocardiography performed within 12 days after the initial performance, most patients were found to have cardiac wall motion abnormalities, and their EF had returned to normal (ie, EF ≥50%).

Conclusions: CO-induced CMP was identified in 3.04% (n=19) of all patients (n=626). It might not be too critical in acute clinical courses of acute CO poisoning because the prognosis seems favorable. Considering the common factors between CO-induced CMP and takotsubo CMP, myocardial stunning subject to a catecholamine surge most likely plays a central role in the development of CO-induced CMP. (*Circ J* 2014; **78:** 1437–1444)

Key Words: Carbon monoxide (poisoning); Cardiomyopathy; Catecholamine; Myocardial stunning; Prognosis

Carbon monoxide (CO) is an odorless, colorless, and non-irritating gas.[1,2] Even a small amount of CO exposure is possibly associated with organ damage and specific toxic effects. Acute CO poisoning is a major cause of mortality and morbidity worldwide.[1,2] According to previous reports, the main mechanism of CO toxicity is ischemic hypoxia secondary to hypoxemia.[1,3,4] Specifically, the heart is the major target organ of acute CO poisoning.[3]

Cardiovascular manifestations demonstrated in previous reports include arrhythmia, pulmonary edema, heart failure, and myocardial infarction.[5–10] Cardiac failure was presented in patients who experienced acute CO poisoning.[8,11] According to Anderson et al,[12] reversible cardiac failure might occur when the carboxyhemoglobin (COHb) level is greater than 25%. Still, the clinical features and the pathophysiology of CO-induced cardiac injury are not completely understood. CO-induced cardiomyopathy (CMP) is not an established concept yet, and reports on its epidemiology and clinical characteristics are scarce. Therefore, clinical characteristics of CO-induced CMP and its significance need to be elucidated.

Stress-induced CMP, also known as takotsubo CMP, is a type of heart failure characterized by rapid reversibility and distinctive contraction patterns in the left ventricle.[13–16] It can be triggered by emotional events, and is found predominantly in postmenopausal women.[13,15] Takotsubo CMP occurs under the condition of catecholamine excess, as in exogenous epinephrine, pheochromocytoma, and acute neurologic disorders (eg, intracranial bleeding and cerebral infarction).[17–21]

There are a number of common factors between CO-induced CMP and takotsubo CMP, although the clinical features are not completely identical. Here, we investigate CO-induced CMP in terms of its epidemiology, clinical characteristics, and prognosis.

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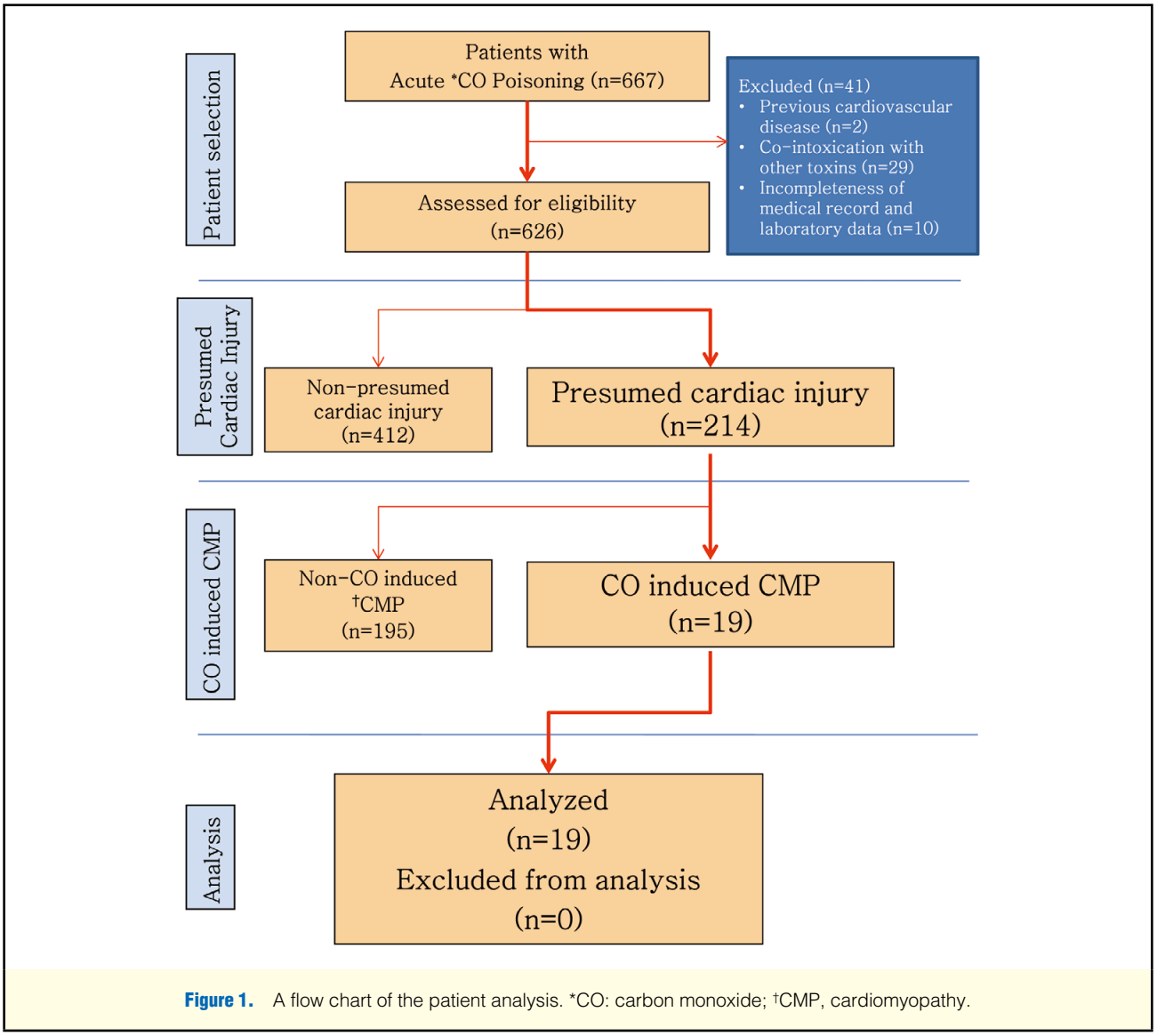


Figure 1. A flow chart of the patient analysis. *CO: carbon monoxide; †CMP, cardiomyopathy.

Methods

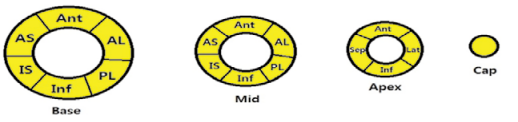
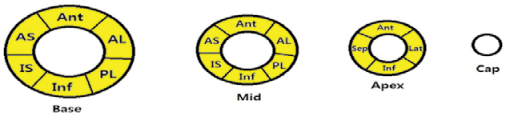
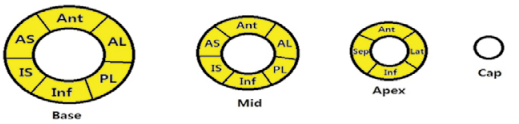
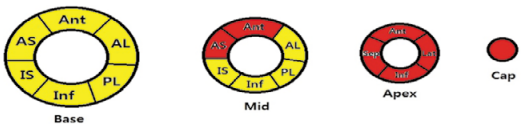
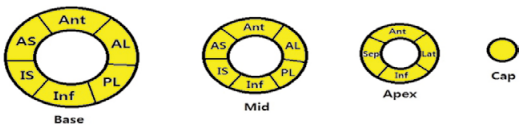
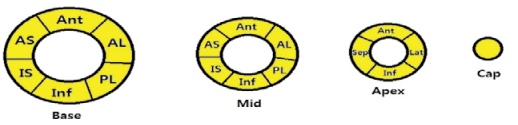
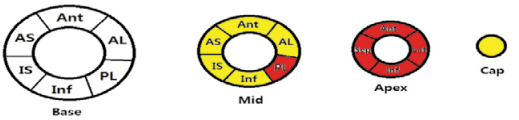
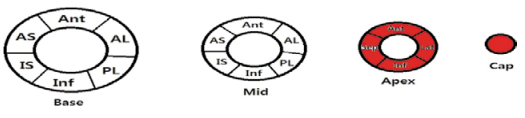
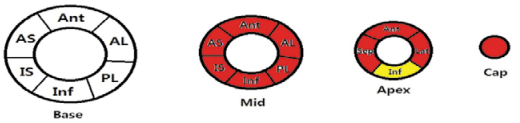
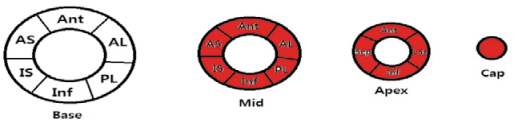
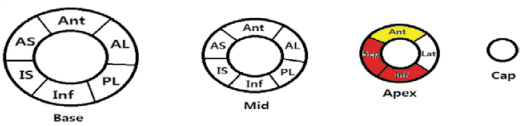
Retrospective data were collected from patients who visited an emergency medical center of Ajou University Hospital during the period of 62 months from August 2008 to September 2013. This study was approved by our institutional review board.

Our selection criterion was diagnosis of acute CO poisoning. Diagnosis was made by studying patient history, clinical characteristics, physical examination and blood COHb. The patients with CO-induced CMP who had been diagnosed with acute CO poisoning were studied. The definition of CO-induced CMP is: (1) transient hypokinesia, akinesia, or dyskinesia of the left ventricular (LV) mid-segments with or without apical involvement after acute CO poisoning; (2) regional wall motion abnormalities extending beyond the geographic territory of a single epicardial artery; (3) absence of obstructive atherosclerotic coronary artery stenosis (<50% luminal narrowing of the epicardial artery); (4) new electrocardiograms (ECG) abnormalities or modest elevation in cardiac troponin; and (5) a complete recovery of regional wall motion abnormalities. Also, transient left ventricular dysfunction syndrome (TLVDS) without coronary artery disease was added to the definition.[22–24] Exclusion criteria included multiple gas intoxication, incomplete medical records, previous cardiovascular disease and no echocardiographic evaluation due to premature expiration after ED admission.

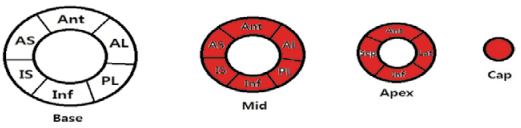
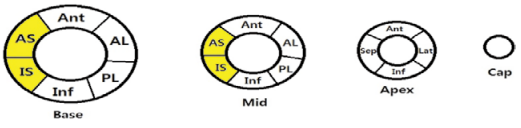
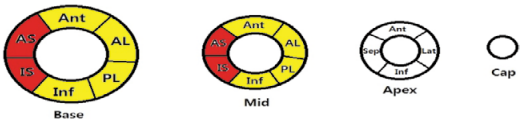
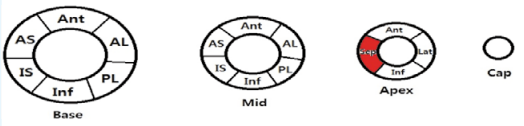
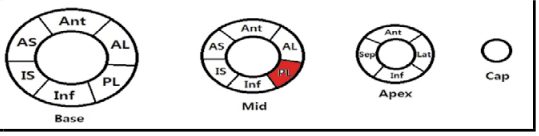
Medical records of the patients were reviewed. Demographic, clinical, and laboratory data were extracted by 2 trained emergency physicians. Laboratory data at the time of admission included cardiac markers [creatine kinase (CK), creatine kinase MB isoenzyme (CK-MB), and troponin T or I], S-100b concentration and COHb concentration. ECG were reviewed separately from the clinical data and were classified according to the rhythm and ST-T wave changes. Ischemic change was defined by a new-onset bundle branch block, other arrhythmias, ST segment elevation (≥1 mm), depression (≥0.5 mm), or T wave inversion (≥2 mm) in 2 consecutive leads. Laboratory-presumed cardiac injury was defined as a CK-MB >5 μg/L, troponin T hs >0.014 ng/ml or troponin I >0.04 ng/ml.

All patients underwent continuous ECG monitoring. Echocardiograms were performed for the patients who showed

Table. Clinical Characteristics and Echocardiography Results in Patients With CO-Induced Cardiomyopathy

	Age (years)	Gender	EKG Changes	Enzyme Elevation Tro I or T / CK-MB (S-100b)	LVEF (%) Initial	LVEF (%) F/U	WMSI Type	Wall Motion Abnormality
1	44	M	Bifascicular B	0.09/ >500 (1.720)	HD2 44		2 G	
2	31	M	ST Change QTc ↑	0.16/8.2 (0.18)	HD1 20	HD12 60	2 G	
3	34	M	ST Change QTc ↑	0.07/ >500 (3.68)	HD1 45		2 G	
4	24	M	ST Change QTc ↑	5.41/21.5 (0.13)	HD1 16	HD6 73	2.38 G	
5	44	M	LBBB	2.07/51.2 (0.32)	HD1 38	HD6 65	2 G	
6	29	M	ST Change	5.69/52.9 (0.44)	HD1 27	HD6 71	2 G	
7	20	M	ST Change	2.22/33.0 (0.35)	HD1 35	HD6 61	2 G	
8	18	F	ST Change QTc ↑	0.44/10.2	HD1 25	HD4 60	1.94 T	
9	26	F	ST Change QTc ↑	0.02/149.1 (1.03)	HD2 48	HD7 65	1.5 T	
10	37	F	ST Change QTc ↑	0.19/35.5 (0.29)	HD1 15	HD7 53	2.25 T	
11	33	F	ST Change	4.91/12.0 (0.11)	HD1 21	HD9 52	2.25 T	
12	75	F	ST Change QTc ↑	0.38/47.2	HD2 47		1.31 T	

(Table continued the next page.)

	Age (years)	Gender	EKG Changes	Enzyme Elevation Tro I or T / CK-MB (S-100b)	LVEF (%) Initial	LVEF (%) F/U	WMSI Type	Wall Motion Abnormality
13	36	F	ST Change QTc ↑	0.09/8.4	HD2 32		2.25 T	
14	42	M	ST Change QTc ↑	0.25/14.2 (0.352)	HD1 53		1.25 RT	
15	22	M	ST Change QTc ↑	30.04/169.0 (0.86)	HD2 25		2 RT	
16	83	F	ST Change QTc ↑	0.09/58.5	HD1 40		1.81 NS	
17	69	M	QTc ↑	0.12/247.9 (0.09)	HD1 45		1.44 NS	
18	43	F	NSR QTc ↑	0.32/25.2 (0.06)	HD1 55	HD4 64	1.12 NS	
19	79	M	QTc ↑	0.39/40.8	HD2 55		1.12 NS	

CO-induced CMP was identified in 3.04% (n=19/626) of all cases in the present study. However, all wall motion abnormalities were recovered at the follow-up echocardiography, which was performed within 12 days after the initial performance.
AL, antero-lateral; Ant, anterior; AS, antero-septal; Bifascicular B, bifascicular block; CK-MB, creatine kinase MB isoenzyme; CMP, cardiomyopathy; CO, carbon monoxide; EKG, electrocardiogram; F/U, follow up; G, global LV dysfunction type; HD, hospital day; Inf, inferior; IS, infero-septal; LBBB, Left Bundle Branch Block; LVEF, left ventricle ejection fraction; NS, non-specific type; PL, postero-lateral; QTc, corrected QT time; RT, reverse Takotsubo type; ST Change, ST elevation, T-wave inversion and ST Depression; T, Takotsubo type; Tro I, troponin I; Tro T, troponin T; WMSI, wall motion severity index.

elevated cardiac enzyme levels (levels of troponin T hs >0.3 ng/ml or troponin I >0.14 ng/ml), ischemic ECG changes, dysrhythmia, or continuous low blood pressure (<90 mmHg systolic). Echocardiograms were classified by ejection fraction (EF) and wall motion abnormalities.

We described our continuous data by their mean and standard deviation. Data were analyzed by using the SPSS 15.0 statistics program (SPSS Inc, Chicago, USA).

Results

Among the 667 patients who were diagnosed with acute CO poisoning, 626 patients were finally selected for this study. A total of 214 patients were assigned to the presumed cardiac injury group. Forty-one patients were excluded due to incomplete medical records, previous cardiovascular diseases, and co-intoxication from other toxins (Figure 1). The gender ratio was 1:0.73 (male : female), and the mean age was 41.7±20.3 years. Poisoning was intentional for 13 patients and accidental for 6 patients. The mean exposure time to CO was 451.1±233.2 min. The mean CO concentration was 20.9±12.9%.

Hypotension (systolic blood pressure below 90 mmHg) was developed in 12 patients (63.2%). ECG abnormalities were shown in 16 patients (84.2%); ST-T wave depression in 4 patients, ST elevation in 7 patients, non-specific ST-T wave changes in 4 patients, and bundle branch block in 1 patient. Cardiac enzyme abnormalities such as CPK, CK-MB, and tro-T elevation were shown in all patients (100%; Table).

Echochardiography was performed in 84 patients, where 65 were normal and 19 were abnormal. Among the 19 abnormal patients, 7 had global LV dysfunction. The remaining 12 patients had regional wall hypokinesia or akinesia, of which 6 had wall motion abnormalities in the mid LV or apex, and 2 had abnormal wall motions saving apex. These results were regarded as similar to the findings for takotsubo CMP and reverse takotsubo CMP, respectively. At the initial echocar-

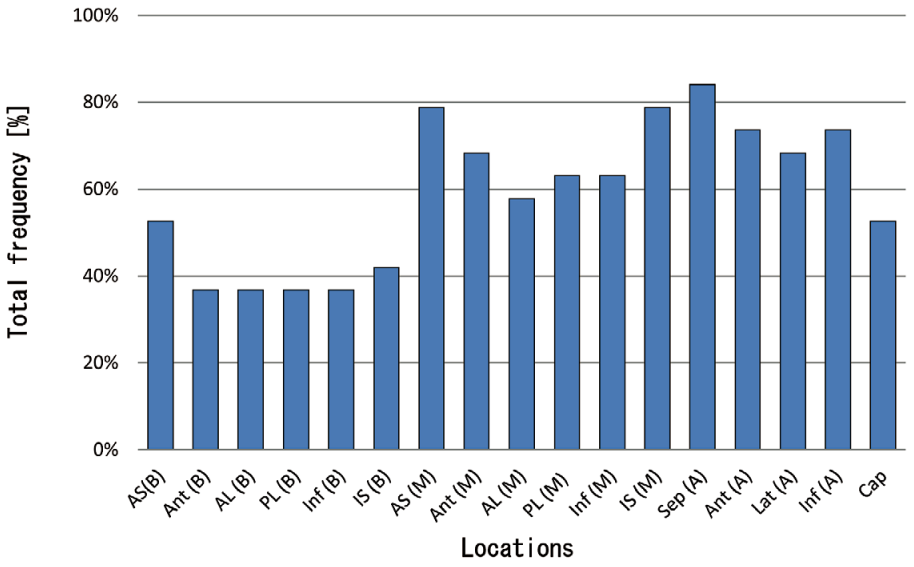


Figure 2. Apex areas were the most frequent locations involved in CO-induced CMP, which was likely to be associated with takotsubo CMP. CO, carbon monoxide; CMP, cardiomyopathy.

diography, the EF was 36.3±13.5%, ranging from 15% to 55%. A follow-up echocardiography was performed in 10 patients within 12 days after the initial echocardiography. Most patients had their EF and abnormalities on wall motion return to normal (ie, EF ≥50%). All the patients who had been diagnosed with CO-induced CMP were discharged alive. Details of the abnormal echocardiographic findings are listed in **Table**. The location of CO-induced CMP in echocardiography is shown in **Figure 2**.

Discussion

To the best of our knowledge, this is the first study investigating CO-induced CMP as a clinical entity. Previous studies about reversible cardiac failure after acute CO poisoning have been reported only through some anecdotal cases.[8,25,26] We found that CO-induced CMP occurred in 3.04% (n=19/626) of the study subjects, and their prognosis was favorable.

CO-Induced CMP

Previous reports have shown that the recovery time from CO-induced CMP varied from 4 days to 6 weeks.[8,25] In the present study, however, all patients showing CO-induced CMP, excluding those patients who expired in the emergency room, recovered mostly within 12 days after admission. Further studies will be needed to clarify why the recovery time was shorter in the present study compared with that reported in previous studies.

In echocardiography, 7 patients had global LV dysfunction and 12 patients had regional wall hypokinesia or akinesia. Six resembled takotsubo CMP, and 2 resembled reverse takotsubo CMP. Based on previous reports of CO-induced myocardial injuries and the present study results,[8,9] we could not fully explain why types, grades of severity, and locations of CO-induced CMP vary in patients with CO-induced CMP. Assuming that there was an identical time duration and concentration of CO exposure, the basic mechanisms of injury seemed to determine how CO-induced CMP develops, as well as individual differences in genetic and hormonal characteristics. Therefore, we think that individual variations in regional myocardial vulnerability might determine the location of regional wall motion abnormality.[27,28] For example, individual patterns of β_2AR expression were likely to be different in the base or mid-left ventricle.[27] According to Mikail et al,[23] transient left ventricular dysfunctional syndromes (TLVDS) seem to include takotsubo CMP and takotsubo-like syndrome. There were distinct discrepancies between normal myocardial perfusion, individual regional myocardial sympathetic innervations, and individual metabolism of epinephrine and norepinephrine in TLVDS.[29–31] These discrepancies were likely to be one reason why CO-induced CMP varies in location, type and severity in terms of clinical characteristics. Acute CO poisoning increases neural output to the sympathetic nervous system via carotid and aortic bodies.[4] These processes are likely to push up the level of catecholamine in synapses of the whole myocardium, which can account for distinct local concentration gradients and phenotypes of catecholamines such as epinephrine and norepinephrine. We speculate that these responses are the physiologic barrier preventing the heart from developing catecholamine-induced myocardial failure or further severe injuries such as acute myocardial infarction under catecholamine excess. If the heart is thoroughly responsive to however much of an increase of catecholamine there may be, catecholamine-induced myocardial failure can occur. Therefore, physiologic mechanisms of the human body temporarily make the heart dysfunctional either globally or regionally.

Differences between CO-induced CMP and takotsubo CMP were identified, although their general features were quite similar. First, chest pain was not as frequent in CO-induced CMP. Plus, ST segment change was not as large as that in patients with stress-induced CMP. Second, stress-induced CMP tends to be more prevalent in postmenopausal women,[15] but there was no gender prevalence in CO-induced CMP. Third, the average age for CO-induced CMP was lower than that of stress-induced CMP. Finally, there was no subject who showed intra-cardiac

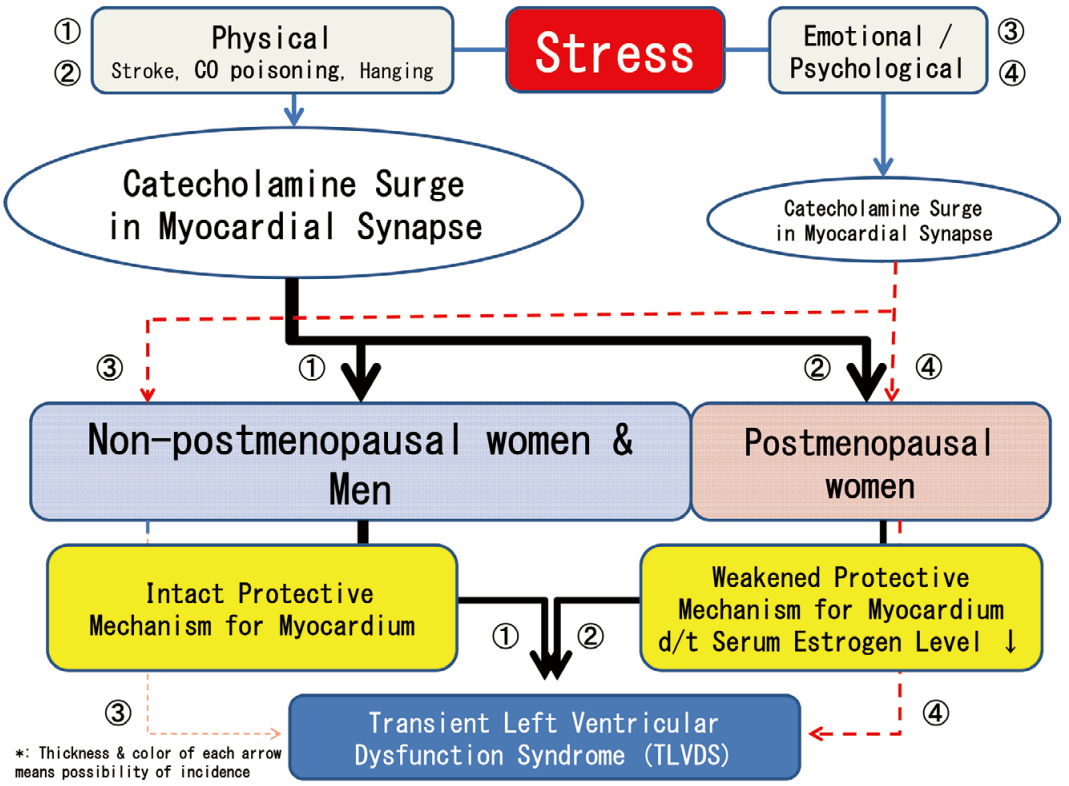


Figure 3. Both physical and emotional stresses result in catecholamine surge (①&②, ③&④, respectively). Physical stress results in a larger degree of catecholamine surge than emotional stress. Here, each stress type can cause TLVDS in patients due to the amount of catecholamine. Stress-induced CMP is more prevalent in postmenopausal women. The reason seems to be associated with a decrease in blood estrogen, meaning weakened protection against catecholamine in the myocardium. Therefore, a relatively small degree of catecholamine surge with emotional stress could lead to the development of TLVDS in postmenopausal women (②&④). In the same way, TLVDS might occur in non-postmenopausal women as well as in some men who experience physical stress (①&③). Acute CO poisoning is a type of stress that causes an exaggerated degree of catecholamine surge due to flow ① and ②, as compared to emotional stress (③&④). Therefore, the possibility of developing TLVDS should be higher in postmenopausal women who experience physical stress (①) and in non-postmenopausal women or men who experience physical stress (②), and only moderately high in postmenopausal women who experience emotional stress (④). It should be the lowest in non-postmenopausal women and men who experience emotional stress (③). TLVDS, transient left ventricular dysfunction syndrome; CMP, cardiomyopathy; CO, carbon monoxide.

thrombus, although some previous studies reported thrombus formation as a major complication in patients with CO-induced CMP.[32,33] Further studies are necessary in order to explain this discrepancy.

Pathophysiology of CO-Induced CMP

The heart and the brain are 2 bodily organs that are most vulnerable to CO-induced hypoxia. This is mainly because of their high demands for oxygen.[2,3] The mechanism of acute CO injury in the heart and the brain might look straightforward, but it has never been clarified. So far, the mechanism of CO-induced cardiac injury or cardiac failure in acute CO poisoning was thought to be stemming from myocardial hypoxemia and possibly from the direct effects of CO on the heart.[3,9] Interestingly, in order to compensate for the lack of oxygen, stimulation of sympathetic nervous system activities increased cardiac output and maintained blood pressure in CO-intoxicated animal models.[4] COHb formation alone is not able to explain CO-related cardiac injury fully. Thus, several additional mechanisms were suggested such as interactions between myoglobin and cytochromes, free radical productions in ischemia reperfusion injury, and disruption of CO's physical functions.[3,34]

Herein, we propose our theory on the pathophysiology of CO-induced CMP. The basic mechanism of CO-induced CMP could be myocardial stunning. Several potential mechanisms of myocardial stunning in CO-induced CMP are described as follows. The most probable cause of myocardial stunning that we suggest is *catecholamine surge*, which results from acute CO poisoning. The potential mechanism of TLVDS, including CO-induced CMP, is shown in **Figure 3**. Wittstein et al. reported that the catecholamine level was found to be elevated in patients with stress-induced CMP, which contributed to the main pathogenesis.[35] Similarly, postmortem catecholamine levels of pericardial and cerebrospinal fluids were measured when acute CO poisoning occurred and were found to be relatively high.[36,37] In takotsubo CMP, a circulating catecholamine such as epinephrine, triggers a switch in high levels from G_s to G_i protein signaling via the β_2-adrenoreceptor in ventricular cardiomyocytes.[38] This change results in a negative inotropic

effect. This negative effect is greatest at the apical myocardium, where the β-adrenoreceptor density is at its highest.[38] After the surge in epinephrine has cleared from the circulation, β_2-adrenoreceptor coupled to G_i proteins either switch back to G_s protein.[27,38] This enables cardiomyocytes to recover their inotropic function. Considering the common factors between CO-induced CMP and takotsubo CMP, we assert that the most probable mechanism of CO-induced CMP would be a catecholamine surge in myocardial synapses.

Second, *histotoxic hypoxia* could be another cause. Previous reports generally considered this as the main mechanism of CO-induced myocardial injury.[30,31,39,40] After the exposure to hypoxia, one's cardiac contraction will decline.[4,7] Tritapepe et al. previously demonstrated histotoxic hypoxia in experimental model with acute CO poisoning.[30] In their study, acute CO poisoning might have caused an alteration of mitochondrial dysfunction in the absence of coronary narrowing.[30] This directly predisposes the myocardial cells to temporary contractile dysfunction due to inhibition of the cytochrome chain.[39] These processes might have resulted in myocardial stunning.[40] Histotoxic injury, unlike the ischemic myocardial damage, is not accompanied by a rapid decrease of intracellular pH.[41] Therefore, injured cardiac function subject to acute CO poisoning might recover after restoration of intracellular oxygenation, and decreasing CO and CO_2 levels.[41]

The third possible cause is *toxic myocarditis*, which results in the transient impairment of myocardial contractility after acute CO poisoning. According to Cupo et al,[42] severe scorpion envenomation led to the development of toxic myocarditis, which resulted in the transient impairment of myocardial contractility. This mechanism, however, should not be the main contributor, even though the clinical features of such a syndrome are similar to those of stress-induced CMP.[43] There were large glycogen deposits in the victim with CO-induced CMP, but this is not typical for myocarditis.[30]

The present study has several limitations. First, the study is retrospective in nature, thus selection bias and incompleteness of the data set might have affected our findings. Second, an autopsy was not performed for those patients who expired soon after ED admission, hence no cardiac toxicity evaluation occurred. Third, it is possible that there has been coronary vasospasm and stenosis in epicardial arteries or myocarditis in the myocardium. Coronary angiography was performed only in 2 subjects, and an endomyocardial biopsy was not performed. Considering the relative young age of the subjects, they are less likely to have had acute coronary syndrome from the time of ED admission until discharge. Fourth, the levels of catecholamines were not identified in our subjects. They are not routinely measured when acute CO poisoning occurred, hence there was no investigation of catecholamine levels in patient with CO-induced CMP. Finally, there is an undeniable possibility of stress-induced CMP because we could not identify the contribution of suicide commitment as part of the emotional stress during the development of takotsubo CMP.

In conclusion, we found that CO-induced CMP occurred in 3.04% of all acute CO poisoning patients. This, by itself, might not be too critical at an acute clinical stage, as the prognosis seems favorable. Myocardial stunning subject to a catecholamine surge most likely plays a central role in the development of CO-induced CMP.

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