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ORIGINAL ARTICLE

Reduced Left Ventricular Ejection Fraction in Acute Carbon Monoxide Intoxication: Associations with Troponin, QT Dispersion, and Short-Term Recovery

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ABSTRACT

Background: Although decreased ejection fraction (EF) is often observed in carbon monoxide (CO) poisoning, this does not equate to the established chronic heart failure category of heart failure with reduced EF (HFrEF).

Aim: The primary objective of this study was to determine the frequency of reduced left ventricular EF (LVEF) during acute CO intoxication and its short-term recovery. Secondary objectives were to evaluate the associations of troponin I, carboxyhemoglobin (COHb, %), and QT dispersion (QTd) with reduced LVEF; the association between troponin I and the timing of LVEF recovery; and the occurrence of clinically evident acute pulmonary edema.

Study Design: This retrospective study included 344 patients with acute CO intoxication.

Methods: LVEF was measured by echocardiography at admission and during follow-up. QTd, cardiac troponin I levels, and clinical signs of acute pulmonary edema were also evaluated. Reduced LVEF was defined as an LVEF of <40% at admission.

Results: A total of 344 patients were included, of whom 217 were female. The mean age was 39.57±15.94 years. Reduced LVEF was observed in 121 patients. Higher COHb, troponin I, and QTd values were independently associated with reduced LVEF [COHb: odds ratio (OR), 1.040; 95% confidence interval (CI), 1.014-1.065; p=0.002; troponin I: OR, 1.093; 95% CI, 1.040-1.151; p=0.001; QTd: OR, 1.120; 95% CI, 1.053-1.192; p<0.001]. On receiver operating characteristic analysis, QTd showed the best discrimination for reduced LVEF [area under the curve (AUC), 0.702; 95% CI, 0.645-0.759], followed by COHb (AUC, 0.640; 95% CI, 0.575-0.705) and troponin I (AUC, 0.590; 95% CI, 0.529-0.651). COHb showed a weak association with reduced LVEF status. Reduced LVEF was weakly correlated with QTd and troponin levels. No significant correlation was found between troponin level and QTd or between troponin level and the timing of LVEF recovery. Additionally, there was no significant difference in the occurrence of acute pulmonary edema between patients with reduced and normal LVEF (2/121 vs. 2/223).

Conclusion: Reduced LVEF was frequently observed during acute CO intoxication and was usually reversible in the short term. Troponin I was associated with reduced LVEF but not with the timing of recovery. QTd was associated with reduced LVEF and showed the highest discrimination among the three variables examined; however, the modest absolute between-group difference and moderate AUC indicate that its clinical utility should be interpreted cautiously and requires further validation. Clinically evident acute pulmonary edema was uncommon in this cohort; the potential effects of CO on pulmonary vascular tone are discussed as a hypothesis-generating consideration rather than as a demonstrated mechanism. Given the retrospective, single-center design and the very small number of pulmonary edema events, these findings should be interpreted as associations rather than as evidence of prognosis or causal protection.

Keywords: Carbon monoxide intoxication, reduced left ventricular ejection fraction, troponin I, QT dispersion, acute pulmonary edema

INTRODUCTION

Carbon monoxide (CO) is a gas that can be produced endogenously in small amounts through heme breakdown. It is odorless and colorless under ambient conditions and does not cause irritation when inhaled. Even low levels of CO inhalation can lead to poisoning and serious organ damage.[1] CO poisoning is a major cause of morbidity and mortality. It has been reported that CO poisoning results in approximately 50,000 emergency department visits and 1,200 deaths each year in the United States.[2]

CO intoxication affects many organ systems, especially the nervous and cardiovascular systems, and myocardial injury is closely related to the severity of poisoning. The severity of symptoms and findings at presentation is closely related to the duration and intensity of CO exposure. Since the main mechanism of CO poisoning is hypoxemia-induced tissue hypoxia and ischemia, it is not surprising that the heart is particularly sensitive to CO. Studies have shown that myocardial damage, which can occur in moderate-to-severe cases, is associated with worse outcomes after CO poisoning.[3,4] Major cardiac

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complications include ventricular dysfunction and severe arrhythmias, which can occur even after exposure to low levels of CO. Although CO primarily acts through direct toxic effects and myocardial hypoxia, various mechanisms have been proposed.[5] Research has demonstrated myocardial dysfunction in patients with CO poisoning, with increased troponin levels and decreased left ventricular EF (LVEF) values.[6,7] Electrocardiograms (ECGs) in these cases often focus on interval and dispersion parameters, whereas ischemic signs are less frequently observed. In this context, the QT interval, QT dispersion (QTd), P-wave measurements, and their associations with arrhythmias are commonly assessed.[8-10] As demonstrated in many studies, myocardial dysfunction is highly reversible with prompt and appropriate treatment.

Although the direct toxic effects of CO intoxication on the lungs have been studied, its primary impact is attributed to hypoxia. Alveolar damage, pulmonary edema, and pneumonia are common findings in many cases. Three mechanisms have been proposed to explain the pulmonary edema observed in CO poisoning. The first emphasizes the direct toxic effects of CO, the second involves its effects through acute heart failure, and the third suggests neurogenic mechanisms.[11] Acute respiratory distress syndrome has also been reported, although rarely. Although a detailed evaluation of pulmonary and cardiac findings in CO poisoning may initially suggest a reduction in EF and related pulmonary edema, studies indicate that the underlying mechanism is more complex. In fact, the correlation between the degree of LVEF reduction and pulmonary findings, or between troponin levels and cardiac findings, has not been definitively established.

Based on these findings, the objective of this study was to determine the frequency of reduced LVEF during acute CO intoxication, characterize its short-term recovery, and examine the associations of troponin I, carboxyhemoglobin (COHb), and QTd with reduced LVEF and LVEF recovery. We also report the frequency of clinically evident acute pulmonary edema in this cohort.

METHODS

This was a retrospective, single-center study. The study protocol was approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval number: 06/38, date: 17.12.2012). The study population included 649 patients admitted to the emergency department of University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital with a diagnosis of CO intoxication during the preceding 3 years. Data were collected from the hospital's electronic medical record system and patient records. Patients aged <18 years, those with incomplete data, and those with a history of heart failure, coronary artery disease, chronic renal failure, chronic obstructive pulmonary disease, cancer, or autoimmune disease were excluded. Of the remaining 523 patients, 118 without echocardiography (ECHO) records and 61 without follow-up ECHO examinations were excluded. Ultimately, the final study sample consisted of 344 patients.

Study Outcomes

The primary outcome of this study was the presence of reduced LVEF (defined as LVEF <40%) on ECHO during the acute presentation. Secondary outcomes were as follows: (i) short-term recovery of LVEF, defined as documented normalization of left ventricular systolic function on follow-up ECHO and categorized according to the time point at which normalization was documented (within 24-48 hours, by day 7, or not documented by day 7); recovery was not defined by a prespecified absolute increase in LVEF; (ii) the associations of troponin I, COHb, and QTd with reduced LVEF; (iii) the association between troponin I and the timing of LVEF recovery; and (iv) the occurrence of clinically evident acute pulmonary edema. This study did not evaluate mortality, major cardiovascular events, neurologic outcomes, or long-term clinical prognosis. Accordingly, troponin I is discussed as a marker of myocardial involvement and reduced LVEF rather than as a general prognostic marker.

Carbon Monoxide/Carboxyhemoglobin Measurement

The laboratory parameter measured was COHb, determined from arterial or venous blood gas samples analyzed using a blood gas analyzer with an integrated co-oximetry module. Results were recorded as a percentage of total hemoglobin (% COHb). Blood sampling was performed at the time of emergency department presentation, before the administration of supplemental oxygen therapy when possible. For patients who had already received oxygen before hospital arrival, the earliest available documented COHb measurement after presentation was used. The unit previously shown as "mg/m³" in the relevant tables was a mislabeling of this same variable and has been corrected to "% COHb" throughout the manuscript, tables, and figures. The terms "CO" and "COHb" are no longer used interchangeably.

Definition of the Reduced LVEF

LVEF was primarily assessed visually, with the Simpson method used in 27 patients. Patients with an LVEF <40% at admission were classified as having reduced LVEF. This threshold was chosen to identify patients with unequivocally reduced systolic function rather than mildly reduced LVEF and represents the operational definition used for the primary outcome of this study. It does not, by itself, establish a clinical diagnosis of chronic heart failure with reduced EF (HFrEF). Throughout this manuscript, we therefore use the terms "reduced LVEF" and, where appropriate, "acute/transient left ventricular systolic dysfunction," rather than HFrEF, which refers to an established chronic heart failure category.

Follow-up ECHO

Acute pulmonary edema was diagnosed using a composite clinical-radiologic definition. For classification as clinically evident acute pulmonary edema in this study, all of the following elements were required: compatible symptoms (paroxysmal nocturnal dyspnea and/or orthopnea), inspiratory rales, interstitial edema on chest computed tomography compatible with acute pulmonary edema, compatible blood gas findings, and regression or improvement of clinical findings after diuretic treatment.

All 121 patients with reduced LVEF at admission underwent follow-up ECHO at 24-48 hours and, if normalization of left ventricular systolic function had not yet been documented, again at 7 days. The 93, 24, and 4 patients reported in the Results (see Table 1) represent mutually

Table 1. LVEF and troponin I values at admission and by recovery-timing subgroup among the 121 patients with reduced LVEF [mutually exclusive groups; see Methods (follow-up echocardiography)]

Recovery timing	n (of 121)	LVEF (%)	Troponin I (ng/mL)
At admission (all 121)	121	31±3.1	31.74±9.73
Recovered within 24-48 h	93	53±7.3	37.23±4.84
Recovered within 7 days (not recovered at 24-48 h)	24	59±9.2	12.11±2.43
No documented normalization by day 7	4	43±10	28.54±1.78

Rows represent mutually exclusive patient subgroups defined by the timepoint at which normalization of left ventricular systolic function was documented, not repeated measurements in the same 121 patients at every timepoint. The admission troponin I value is 31.74±9.73 ng/mL. LVEF: Left ventricular ejection fraction

exclusive categories defined by the time point at which normalization was documented, rather than repeated measurements performed identically in the same 121 patients at every time point: 93 patients had documented normalization within 24-48 hours and were not reexamined at day 7; 24 had not normalized at 24-48 hours but had documented normalization by day 7; and 4 had no documented normalization by day 7. Table 1 is presented accordingly, with the number of patients contributing to each reported value shown explicitly.

Troponin I Assay

Cardiac troponin I was measured using an automated immunoassay analyzer and interpreted using the laboratory-specific 99th-percentile upper reference limit; results are expressed in ng/mL. The admission value refers to the measurement obtained at presentation, and follow-up troponin values were obtained at the corresponding follow-up assessments. For between-group comparisons, correlation analyses, multivariable logistic regression, and receiver operating characteristic (ROC) analysis evaluating reduced LVEF, the admission troponin I value was used; peak troponin I was not used for these analyses.

QTd Methodology

Standard 12-lead resting ECGs were obtained from all patients at presentation and recorded at 25 mm/s with a calibration of 10 mm/mV (1 mV=10 mm). Recordings in which fewer than 8 leads were clearly readable were excluded from QTd analysis. The QT interval was measured from the onset of the QRS complex to the point at which the T wave returned to the isoelectric line; when the end of the T wave could not be clearly identified, the tangent method was applied. The corrected QT interval (QTc) was calculated using Bazett's formula ($QTc=QT/\sqrt{RR}$). QTd ($QTd=QT_{max}-QT_{min}$) and corrected QTd ($QTcd=QTc_{max}-QTc_{min}$) were both calculated in milliseconds as the difference between the maximum and minimum values across evaluable leads; QTd was the parameter reported in the Results. ECG measurements were performed by two independent investigators blinded to clinical data, and interobserver agreement was assessed using the intraclass correlation coefficient.

Statistical Analysis

Statistical analyses were conducted using SPSS version 22.0 (Statistical Product and Service Solutions for Windows, IBM Corp., Armonk, NY; 2013). Results were expressed using descriptive statistics: mean±standard deviation for continuous variables with a normal distribution, median with minimum and maximum values for continuous variables without a normal distribution, and counts and percentages for categorical variables. Pearson's chi-square test was used to compare categorical variables between groups, with Fisher's exact test used where appropriate. For comparisons of numerical variables between two independent groups, Student's t-test was used for variables with a normal distribution, and the Mann-Whitney U test was used for variables without a normal distribution. Spearman's correlation test (ρ) was used to assess correlations between continuous variables and between continuous variables and reduced-LVEF status; the coding and direction of each variable entered into these analyses are stated in the relevant table footnotes. Logistic regression and ROC curve analyses were conducted separately for variables found to be significant in univariate analyses. Logistic regression results are reported as odds ratios (ORs) with 95% confidence intervals (CIs), and ROC results are reported as the area under the curve (AUC) with a separately calculated 95% CI; these two sets of CIs are not interchangeable. In the original multivariable logistic regression model, normal LVEF was coded as the event category. For clinical interpretability, the reported ORs and their 95% CIs were reexpressed toward reduced LVEF by taking their reciprocals; the Wald statistics and p values were unchanged. Variables entered into the multivariable model were those significantly associated with reduced LVEF on univariate analysis (Table 2): COHb, troponin I, and QTd. All statistical tests were 2-sided, and a p value <0.05 was considered statistically significant.

RESULTS

Of the 344 patients included in the study, 217 (63.1%) were female. The mean age of the sample was 39.57±15.94 years (range, 18-78 years). ECHO findings showed reduced LVEF in 121 (35.2%) patients. All 121 patients with reduced LVEF underwent follow-up ECHO at 24-48 hours and, when normalization had not yet been documented, again at 7 days; troponin levels were measured at each assessment. Normalization of left ventricular systolic function was documented within 24-48 hours in 93 (76.9%) patients, who were not reexamined at day 7. Among the remaining 28 patients, normalization was documented by day 7 in 24 (19.8%), whereas it was not documented by day 7 in 4 (3.3%) patients (Figure 1; Table 1). Among the patients with reduced LVEF, 27 had global and 94 had segmental wall motion abnormalities.

Univariate comparisons of factors associated with reduced LVEF are summarized in Table 2. Reduced LVEF was significantly associated with higher COHb ($p=0.003$), troponin I ($p<0.001$), and QTd ($p<0.001$) values.

Clinical symptoms and signs of acute pulmonary edema were observed in 2 of 121 patients with reduced LVEF and 2 of 223 patients with normal LVEF. The difference was not statistically significant.

Multivariable logistic regression, restricted to the variables significant in univariate analysis, showed that higher COHb, troponin I, and QTd values were each independently associated with reduced LVEF: COHb (OR, 1.040; 95% CI, 1.014-1.065; p=0.002), troponin I (OR, 1.093; 95% CI, 1.040-1.151; p=0.001), and QTd (OR, 1.120; 95% CI, 1.053-1.192; p<0.001) (Table 3a). These ORs were reexpressed in the direction of reduced LVEF by taking the reciprocals of the original estimates, in which normal LVEF had been coded as the event; the Wald statistics and p values were unchanged. ROC curve analysis of the same three variables, reported separately from the regression results, showed AUC values of 0.640 [standard error (SE), 0.033; 95% CI, 0.575-0.705] for COHb, 0.590 (SE, 0.031; 95% CI, 0.529-0.651) for troponin I, and 0.702 (SE, 0.029; 95% CI, 0.645-0.759) for QTd (Table 3b; Figure 2), indicating that QTd had the best discrimination for reduced LVEF among the three variables.

Spearman correlation analysis (ρ) showed that COHb level was weakly associated with reduced-LVEF status (ρ=0.149; p=0.006) and QTd (ρ=0.145; p=0.007), but not with troponin level (ρ=0.016; p=0.761). Reduced-LVEF status was weakly correlated with QTd (ρ=0.337; p<0.001) and very weakly correlated with troponin level (ρ=0.235; p<0.001). There was no significant correlation between troponin level and QTd (ρ=0.062; p=0.249) (Table 4).

There was also no significant correlation between troponin level and the timing of LVEF recovery (ρ=0.032; p=0.341) (Table 5).

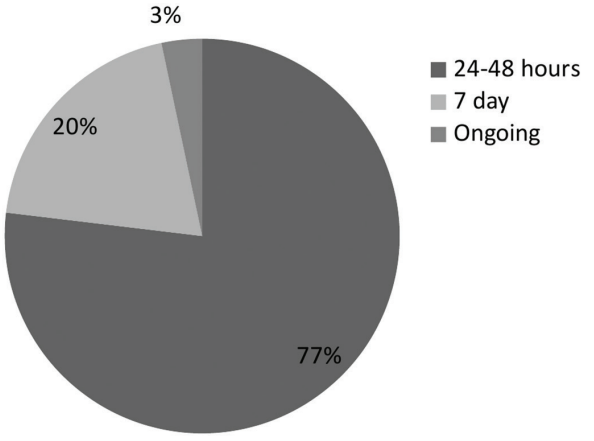

Figure 1. Course of LVEF recovery on follow-up echocardiography among the 121 patients with reduced LVEF at admission. Normalization of left ventricular systolic function was documented within 24-48 hours in 93 (76.9%) patients and by day 7 in 24 (19.8%) patients; normalization was not documented by day 7 in 4 (3.3%) patients. LVEF: Left ventricular ejection fraction

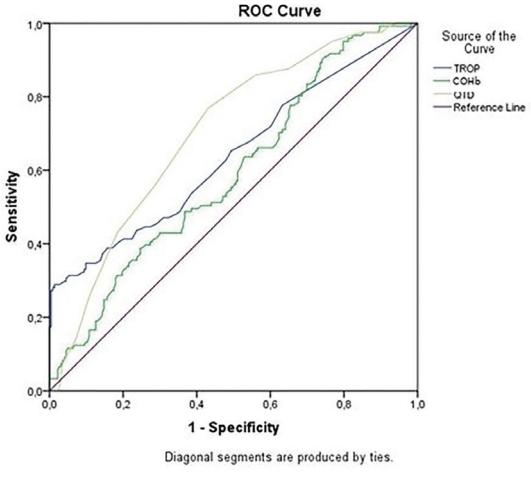

Figure 2. Receiver operating characteristic (ROC) curves for COHb, troponin I, and QTd for discrimination of reduced LVEF. The AUCs were 0.640 for COHb, 0.590 for troponin I, and 0.702 for QTd. QTd: QT dispersion, COHb: Carboxyhemoglobin, LVEF: Left ventricular ejection fraction, AUC: Area under the curve

Table 2. Parameters associated with reduced LVEF

Parameters	Reduced LVEF (n=121)	Normal LVEF (n=223)	p value
Age (years)	38.90±15.65	39.89±16.33	0.587
Gender (female)	78 (64%)	139 (62%)	0.696
COHb (%)	25.46±10.60	21.94±10.35	0.003
WBC (thousand/mm^3)	9.96±6.50	10.21±3.51	0.642
Hemoglobin (g/dL)	13.87±1.75	13.91±2.65	0.877
Hematocrit (%)	40.65±7.31	39.91±9.11	0.771
Platelet (thousand/mcL)	287.14±83.43	270.97±78.90	0.076
MPV (fL)	7.72±1.12	7.90±1.10	0.153
Neutrophil (thousand/mcL)	10.92±14.24	9.23±12.36	0.594
Lymphocyte (thousand/mcL)	3.06±4.95	2.96±4.46	0.854
Glucose (mg/dL)	131.99±53.23	130.27±55.14	0.778
Urea (mg/dL)	38.54±9.71	36.87±10.54	0.149
Creatinine (mg/dL)	0.93±0.33	0.90±0.33	0.537
Sodium (mEq/L)	132.39±6.58	131.89±6.49	0.489
Potassium (mEq/L)	4.74±0.75	4.79±0.76	0.567
Calcium (mg/dL)	11.13±1.75	11.15±1.72	0.901
CK (U/L)	117.35±152.09	129.24±142.23	0.479
CK-MB (IU/L)	26.31±64.46	17.83±11.59	0.057
Troponin I (ng/mL)	31.74±9.73	0.41±3.23	<0.001
QTd (ms)	52.86±2.53	50.43±5.71	<0.001

COHb was measured by co-oximetry on blood-gas analysis and is reported as % of total hemoglobin [see Methods (carbon monoxide/carboxyhemoglobin measurement)]; the unit shown previously as "mg/m^3" was a mislabeling of this same variable. Troponin I value corrected as noted under Table 1. CK, CK-MB, and neutrophil values show wide dispersion and are retained as mean±SD; these summaries should therefore be interpreted cautiously. LVEF: Left ventricular ejection fraction, WBC: White blood cell, MPV: Mean platelet volume, CK: Creatine kinase, CK-MB: Creatine kinase myocardial band, QTd: QT dispersion, SD: Standard deviation, COHb: Carboxyhemoglobin

Table 3a. Multiple logistic regression: factors independently associated with reduced LVEF (odds ratios re-expressed in the direction of reduced LVEF)

Parameter	B	SE	Wald	OR [Exp(B)]	95% CI (OR)	p value
COHb (%)	0.039	0.013	9.492	1.040	1.014-1.065	0.002
Troponin I (ng/mL)	0.089	0.026	11.960	1.093	1.040-1.151	0.001
QTd (ms)	0.113	0.032	12.846	1.120	1.053-1.192	<0.001

Odds ratios and their 95% confidence intervals are expressed in the direction of reduced LVEF, that is, as the reciprocals of the values from the original SPSS output in which normal LVEF was coded as the event. The corresponding B coefficients therefore change sign, whereas the standard errors, Wald statistics, and p values remain unchanged. LVEF: Left ventricular ejection fraction, OR: Odds ratio, CI: Confidence interval, SE: Standard error

Table 3b. ROC curve analysis of factors associated with reduced LVEF (reported separately from the regression results)

Parameter	AUC	SE	95% CI (AUC)
COHb (%)	0.640	0.033	0.575-0.705
Troponin I (ng/mL)	0.590	0.031	0.529-0.651
QTd (ms)	0.702	0.029	0.645-0.759

The 95% confidence intervals shown are specific to the AUC and are distinct from the odds ratio confidence intervals reported in Table 3a. Regression p values are not reported in the ROC table. AUC: Area under the curve, SE: Standard error, CI: Confidence interval, QTd: QT dispersion, COHb: Carboxyhemoglobin, ROC: Receiver operating characteristic, LVEF: Left ventricular ejection fraction

Table 4. Spearman's rho (ρ) correlations among COHb, reduced-LVEF status, troponin I, and QTd

Parameters		COHb (%)	Reduced-LVEF status	Troponin I	QTd
COHb (%)	ρ	1.000	0.149**	0.016	0.145**
	p		0.006	0.761	0.007
Reduced-LVEF status	ρ	0.149**	1.000	0.235**	0.337**
	p	0.006		<0.001	<0.001
Troponin I	ρ	0.016	0.235**	1.000	0.062
	p	0.761	<0.001		0.249
QTd	ρ	0.145**	0.337**	0.062	1.000
	p	0.007	<0.001	0.249	

**Correlation is significant at the 0.01 level (2-tailed). Coefficients are reported as Spearman's rho (ρ), not r. Reduced-LVEF status denotes the binary outcome used in this correlation analysis; p values previously reported as 0.000 are now reported as <0.001. QTd: QT dispersion, COHb: Carboxyhemoglobin, LVEF: Left ventricular ejection fraction

Table 5. Spearman's rho (ρ) correlation between troponin I level and the timing of LVEF recovery

Parameters		Troponin I	LVEF recovery timing
Troponin I	ρ	1	0.032
	p	-	0.341
LVEF recovery timing	ρ	0.032	1
	p	0.341	-

Column/row relabeled from "improvement in EF" to "LVEF recovery timing" for consistency with the outcome definition in Methods (study outcomes). LVEF: Left ventricular ejection fraction, EF: Ejection fraction

DISCUSSION

The principal findings of this study are, first, that reduced LVEF was frequent among patients with acute CO intoxication but usually recovered in the short-term; second, that troponin I was associated with reduced LVEF but not with the timing of recovery; third, that QTd was associated with reduced LVEF and showed the best discrimination among the three variables examined; and fourth, that clinically evident acute pulmonary edema was uncommon and that its mechanism in this setting remains uncertain.

It is known that CO intoxication can reduce LVEF through several mechanisms. The most significant of these involves the sensitivity of organs with high oxygen demands, such as the heart, to hypoxia.[12] The primary cause of hypoxia is the binding of CO to hemoglobin

with a much higher affinity than oxygen. Additionally, CO has direct toxic effects on mitochondria, decreases glutathione levels, and affects intracellular oxidative energy metabolism.[13,14] Evidence also suggests that another mechanism that may contribute to decreased LVEF involves increased catecholamine levels, with similarities to Takotsubo syndrome observed both pathophysiologically and echocardiographically.[15-18] Consistent with the existing literature, we found reduced LVEF in 121 of 344 patients, with global and segmental wall motion abnormalities present in 27 and 94 patients, respectively; reported frequencies vary considerably across studies of CO intoxication, as expected given the heterogeneity in exposure severity and diagnostic thresholds used.[4,6,14,16,19-21]

Only 4 of 344 patients in this cohort had clinically evident acute pulmonary edema (2 with reduced LVEF and 2 with normal LVEF). This number is too small to support conclusions about an association between reduced LVEF and pulmonary edema or about a protective pulmonary effect of CO. Although experimental literature has described pulmonary vascular and neurogenic mechanisms that may influence edema formation in CO intoxication,[11,22-30] these mechanisms were not directly assessed in our study and are mentioned only as possible explanations. No causal or protective pulmonary effect of CO can be inferred from our observations.

It has been shown that cardiac troponin levels correlate with ECHO and ECG findings in CO intoxication,[19] and troponin I has been reported as a marker of myocardial injury with some predictive value for short-term outcomes;[31,32] its correlation with long-term outcomes appears weaker, and markers such as B-type natriuretic peptide/N-terminal pro-BNP (BNP/NT-proBNP) have been suggested as potentially more informative, either alone or in combination with troponin.[33,34] In this study, troponin I was significantly associated with reduced LVEF ($\rho=0.235$; $p<0.001$) but was not correlated with the timing of subsequent LVEF recovery ($\rho=0.032$; $p=0.341$). A decrease in LVEF was observed in 35.2% of patients, with recovery documented in 117 of 121 patients with an initial decrease; however, troponin level did not predict which patients would recover faster.

QTd and QTc reflect ventricular repolarization heterogeneity and are known to increase in patients with CO intoxication.[8-10,17,35,36] Consistent with prior literature, QTd was associated with reduced LVEF in our cohort and showed the highest discriminative performance among the three variables examined (AUC, 0.702). However, the absolute between-group difference in QTd was modest (52.86±2.53 vs. 50.43±5.71 ms), and an AUC of 0.702 represents only moderate discrimination. QTd should therefore be regarded as a potentially useful ECG marker that may complement clinical assessment rather than as an established prognostic parameter or stand-alone discriminator.

Study Limitations

This study has several limitations. First, its retrospective, single-center design means that the regression findings reflect statistical associations rather than causation, and residual confounding cannot be excluded. Second, several clinically important variables were not systematically incorporated into the analysis, including the Glasgow Coma Scale, lactate, blood pH, duration of CO exposure, timing of blood sampling relative to exposure, oxygen treatment modality (normobaric vs. hyperbaric), need for mechanical ventilation or vasopressors, neurologic complications, length of hospitalization, and in-hospital mortality. Their absence limits our ability to draw conclusions about overall poisoning severity and clinical prognosis and may have resulted in residual confounding of the reported associations. Third, LVEF was determined predominantly by visual assessment, with the Simpson method used in only 27 patients. This approach may introduce interobserver and intraobserver variability, and operator-level consistency across serial examinations was not documented in the study report; this should therefore be considered a methodological limitation. Fourth, although patients with a known history of coronary artery disease were excluded, coronary anatomy was not systematically evaluated in all patients. Therefore, occult coronary disease cannot be completely excluded as a contributor to the segmental wall motion abnormalities observed. The study was not designed for a prespecified comparison of the segmental and global wall motion subgroups; therefore, a post-hoc subgroup analysis was not introduced in this revision.

Fifth, BNP or NT-proBNP levels were not measured, which would have provided complementary information on the relationship between ventricular dysfunction and pulmonary congestion. Sixth, only four patients developed clinically evident acute pulmonary edema, which is too few to support firm conclusions about its relationship with reduced LVEF or a potential protective pulmonary effect of CO; accordingly, the mechanistic discussion of this finding should be considered hypothesis-generating. Finally, the primary contribution of this study lies in characterizing the coexistence and short-term course of reduced LVEF, troponin elevation, QTd abnormalities, and pulmonary edema in a relatively large CO intoxication cohort rather than in establishing a new biomarker or prognostic model. Findings extending beyond these observations should therefore be interpreted with caution.

CONCLUSION

In this retrospective cohort, reduced LVEF was frequently observed during acute CO intoxication and was usually reversible in the short-term. Troponin I was associated with reduced LVEF but did not predict the timing of recovery. QTd was associated with reduced LVEF and showed the highest discrimination among the three variables examined; however, the modest absolute difference between groups and moderate AUC support viewing it as a potentially useful adjunctive ECG marker rather than an established prognostic parameter. Clinically evident acute pulmonary edema was uncommon in this cohort. The potential effects of CO on pulmonary vascular tone are discussed as a hypothesis rather than as a demonstrated mechanism, and no causal or protective pulmonary effect of CO is inferred from these observations. Given the observational design, these findings should be regarded as hypothesis-generating and warrant confirmation in larger, prospective studies rather than being interpreted as evidence of long-term prognosis or a treatment effect.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethics Committee (approval number: 06/38, date: 17.12.2012).

Informed Consent: Given the retrospective nature of the study, written informed consent was not required and was waived.

Authorship Contributions: Concept: O.A., Design: O.A., Data Collection or Processing: O.A., S.Y., Analysis or Interpretation: O.A., S.Y., Literature Search: O.A., Writing: O.A., S.Y.

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