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Comparison of Inflammatory and Oxidative Stress Markers Among Patients with Non-Obstructive vs. Obstructive Coronary Artery Disease

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ABSTRACT

BACKGROUND.
Myocardial infarction with non-obstructive coronary artery disease (MINOCA) accounts for 5-20% of all cases of myocardial infarction. The growing evidence indicates the importance of oxidative stress and chronic inflammation in the heterogenous pathophysiology of MINOCA.

OBJECTIVES
In the present study, we aimed to evaluate oxidative and inflammatory statuses in patients with MINOCA and compare them with the same indices of patients with obstructive coronary disease non-ST-elevation acute coronary syndrome (NSTE-ACS).

METHODS
Overall, 165 of 1018 patients admitted to the Coronary Care Unit of Tsinamdzgvrishvili Center of Cardiology LTD (Tbilisi, Georgia) because of the first episode of acute coronary syndrome (ACS) was divided into two groups: 115 patients with MINOCA were distributed into the group 1, and 50 patients with obstructive coronary disease NSTE-ACS into the group 2. Oxidative stress and inflammatory markers were evaluated in study patients.

RESULTS
We found an increase in free radical concentrations in both groups of study patients, but there was no difference in the mean amount of overall organic radicals (FORT)(p=0.412). We also found a significantly lower mean concentration of plasmatic antioxidant compounds (FORD) in patients with MINOCA (p=0.036) compared with NSTE-ACS patients, indicating a more pronounced depletion of antioxidant potential in MINOCA patients. The results of admission inflammatory markers, such as hs-CRP and hemogram-derived NLR, suggest significantly higher inflammatory status in MINOCA patients than in those with NSTE-ACS.

CONCLUSIONS
The results of the present study emphasize the significance of oxidative stress and inflammation in the pathogenesis of MINOCA.

KEYWORDS
Free Oxygen Radical Defense (FORD); Free Oxygen Radical Test (FORT); Myocardial infarction with non-obstructive coronary artery disease (MINOCA); Oxidative profile; Oxidative stress; Oxidative-reductive balance (REDOX index).

BACKGROUND

A significant proportion of patients with coronary heart disease have non-obstructive coronary atherosclerosis and many develop myocardial infarction or MINOCA (myocardial infarction with non-obstructive coronary artery disease), which accounts for 5-20% of all cases of myocardial infarction.[1]

The understanding of the pathogenesis of MINOCA is still incomplete and includes coronary (microvascular disease, rupture of the non-obstructive plaque; coronary spasm, dissection, emboly or thrombosis) and noncoronary mechanisms (myocarditis, Takotsubo cardiomyopathy, etc.).[2,3]

According to the accumulated evidence, oxidative stress and inflammation are crucial for the development of atherosclerosis, its progression, and complications.[4-7]

By triggering endothelial activation, oxidative stress causes endothelial dysfunction with a broad spectrum of consequences, such as impaired vasodilation and abnormal vascular reactivity; expression of chemotactic/adhesive molecules; increased platelet activation and thrombus formation; increased vascular permeability; proliferation and migration of smooth muscle cells; monocyte migration, white blood cell adhesion, and impaired regeneration.[7-21]

In the present study, we aimed to evaluate oxidative and inflammatory statuses in patients with MINOCA and compare them with the same indices of patients with obstructive coronary disease non-ST-elevation acute coronary syndrome (NSTE-ACS).

METHODS

Patient population

Overall, 165 of 1018 patients admitted to the Coronary Care Unit of Tsinamdzgvrishvili Center of Cardiology LTD (Tbilisi, Georgia) because of the first episode of an acute coronary syndrome (ACS) classified as MINOCA or non-ST-elevation acute coronary syndrome (NSTE-ACS) with obstructive coronary disease were included in the study between March 2018 and Aug 2019. The study population was divided into two groups: 115 patients with MINOCA were distributed into group 1, and 50 patients with obstructive coronary disease NSTE-ACS into group 2.

The study protocol was reviewed and approved by the Ethic Committees of Tbilisi State Medical University (TSMU) and Tsinamdzgvrishvili Center of Cardiology LTD, and written informed consent was provided by each study participant.

Evaluation of oxidative markers

CR3000 FORM PLUS (Callegari Srl, Catellani Group, Italy) - analytical module (sample type: whole blood; technique: point of care analysis via ready-to-use, wet, disposable reagents; wavelength: 505 nm) was used for the measurement of the following admission indices: [22]

- Free Oxygen Radical Test (FORT) for the quantitive assessment of overall organic radicals, e.g., Hydroperoxides (ROOHs)/Reactive oxygen species (ROS) by a colorimetric method based on the Fenton reaction with reference range up to 310 Fort units/2.36 mmol/l H2O2 eq;
- Free Oxygen Radical Defense (FORD) for the quantitative assessment of plasmatic antioxidant compounds, including vitamin C; proteins (e.g., albumin and ceruloplasmin); bilirubin; thiol groups (e.g., glutathione); polyphenolic compounds (e.g., flavonoids and tannins) by a colorimetric method based on the quenching of the color with a reference range of 1.07-1.53 mmol/l Trolox eq.;
- Oxidative-reductive balance (REDOX index) - overall score of the oxidation-reduction state, which was expressed as a number (from 0 to 100) identifying five specific profiles (A-E):
  - A. Ideal/normal values: FORT <300 units/2.36 mmol/l H2O2 eq.; FORD ≥1.08 mmol/l Trolox eq; redox index: 0-25;
  - B. Latent oxidative stress: FORT <300 units/2.36 mmol/l H2O2 eq; FORD ≤1.07 mmol/l Trolox eq.; redox index: 25-50;
  - C. Compensated oxidative stress: FORT <330 units/2.36 mmol/l H2O2 eq; FORD ≥1.08 mmol/l Trolox eq.; redox index: 50-58.3;
  - D. At risk of oxidative stress: 300< FORT <330 units/2.36 mmol/l H2O2 eq; FORD ≤1.07 mmol/l Trolox eq.; redox index: 58.3-66.6;
  - E. Oxidative stress in progress: FORT ≥331 units/2.36 mmol/l H2O2 eq; 0.25< FORD <3.00 mmol/l Trolox eq.; redox index: 66.6-100.

Evaluation of inflammatory markers

Admission hemogram-derived lymphocyte-to-neutrophil ratio (NLR) and serum high-sensitivity C-reactive protein (hs-CRP) were measured to assess the inflammatory status of study patients. Roche Cobas 6000 (c501 module) was used for the hs-CRP quantification with the reference range of < 1.0 mg/dL or < 10.0 mg/L.

Statistical analysis

IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA) was used for analyzing data. The differences between groups of patients had assessed by the independent-sample T-test, nonparametric Mann-Whitney U test, and descriptive statistics. A statistical significance was taken as a $p<0.05$.

RESULTS

Patient characteristics

There was no significant difference between the comparator groups concerning age, BMI, smoking status, HbA1c, GFR, ejection fraction (EF), history of AF, or COPD, and previous medications. The proportion of female patients, hypertension, history of ASCVD and chronic liver disease was significantly lower in group 1 (MINOCA patients) compared to the group 2 patients with NSTE-ACS (37% vs. 58%, p=0.011; 61% vs. 82%, p=0.008; 0% vs. 8%, p=0.007 and 0% vs. 4%, p=0.031, respectively). The mean LDL-C concentration also was significantly lower in patients with MINOCA (105.90±22.2 mg/dL vs. 115.96±15.0 mg/dL, p=0.011) (Tab.1).

TABLE 1. Baseline characteristics of patients with MINOCA (group 1) and NSTE-ACS patients with obstructive coronary artery disease (group 2)

	MINOCA n=115	***NSTE-ACS n=50***	***P value***
Mean age, year, M±SD	59.8±5.78	63.2±4.89	0.315
Female, n (%)	42 (37)	29 (58)	**0.011**
Mean age of female patients, year, M±SD	60.07±6.38	62.62±4.78	0.170
Mean BMI, kg/m^2, M±SD	27.1±2.64	26.6±2.94	0.398
Current smoking, n (%)	33 (29)	20 (40)	0.154
Hypertension, n (%)	70 (61)	41 (82)	**0.008**
Mean HbA1c, M±SD	6,2±1.65	6.5±1.64	0.144
Mean EF, %, M±SD	51.7±5.48	51.6±6.07	0.328
History of ASCVD, n (%)	0 (0)	4 (8)	**0.007**
History of AF, n (%)	9 (7.8)	5 (10)	0.646
History of COPD, n (%)	2 (2)	2 (4)	0.387
History of chronic liver disease, n (%)	0 (0)	2 (4)	**0.031**
Mean LDL-C, mg/dL, M±SD	105.90±22.2	115.96±15.0	**0.011**
Mean GFR, mL/min/1.73 m2, M±SD	83.98±9,80	85.26±10.5	0.461
Previous ACIs/ARBs, n (%)	28 (24)	9 (18)	0.370
Previous BBs, n (%)	9 (8)	9 (18)	0.128
Previous CCBs, n (%)	7 (6)	6 (12)	0.196
Previous Statins, n (%)	26 (23)	7 (14)	0.336

Abbreviations: ACIs: Angiotensin-converting enzyme inhibitors; AF: Atrial fibrillation; ARBs: Angiotensin receptor blockers; ASCVD: Atherosclerotic cardiovascular disease; BB: Beta-blockers; BMI: Body mass index; CCB: Calcium channel blockers; EF: Left ventricle ejection fraction; GFR: Glomerular filtration rate; LDL-C: low-density

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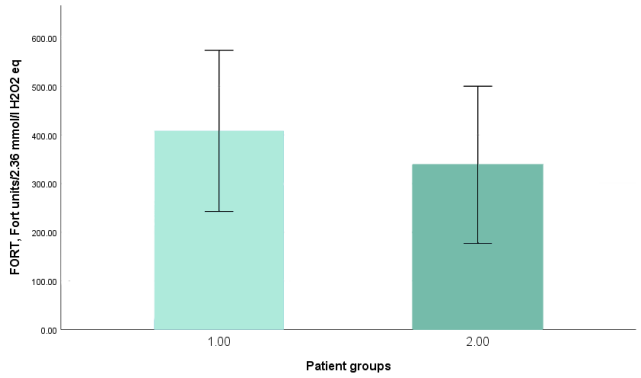
lipoprotein cholesterol; M±SD: mean ± standard deviation; NOCAD: Non-obstructive coronary artery disease.

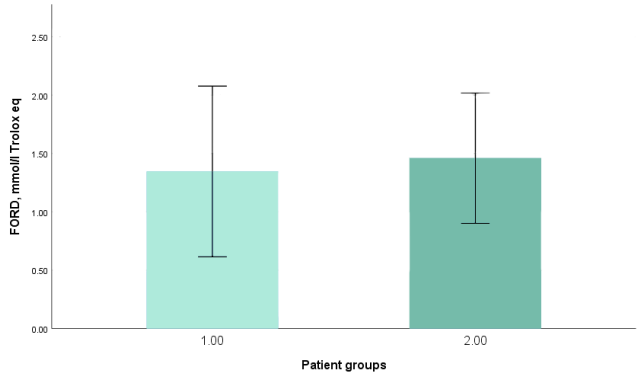
Admission oxidative parameters

Figure 1 and Figure 2 represent the mean admission oxidative/reductive indices of study patients.

FIGURE 1. The mean admission FORT and FORD in different groups of study patients



	MINOCA n=115	NSTE-ACS n=50	P value
FORT, Fort units/2.36 mmol/l H2O2 eq, M±SD	408.4±82.8	333.9±80.7	0.412



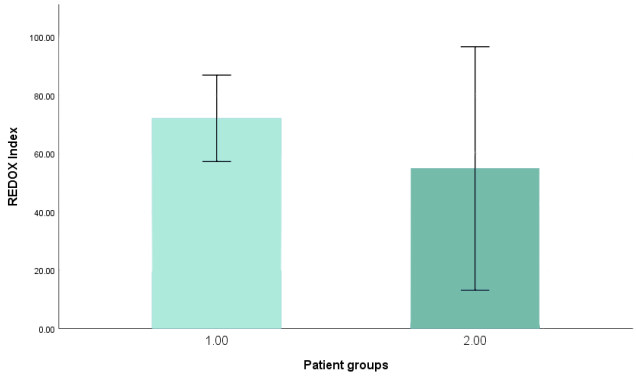
	MINOCA n=115	NSTE-ACS n=50	P value
FORD, mmol/l Trolox eq, M±SD	1.35±0.37	1.46±0.28	**0.036**

Abbreviations: FORD: free oxygen radical defense; FORT: free oxygen radical test; M±SD: mean ± standard deviation.

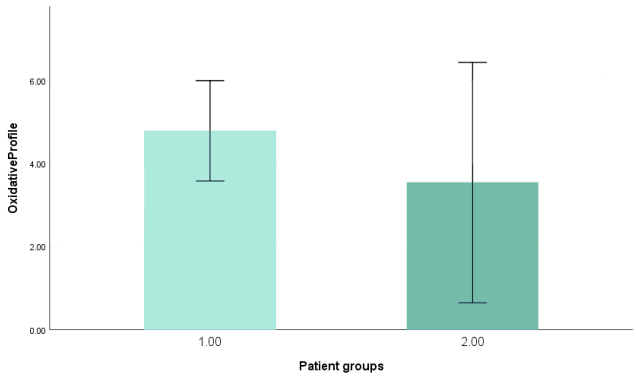
The free oxygen radical test (FORT, Fort units/2.36 mmol/l H2O2 eq.) indices in the group of MINOCA patients (group 1) did not significantly differ from the comparative group 2 patients with NSTE-ACS (408.4±82.8 Fort units/2.36 mmol/l H2O2 eq. vs. 333.9±80.7 Fort units/2.36 mmol/l H2O2 eq., p=0.412). However, free oxygen radical defense (FORD) indices were significantly lower in the first group of patients with MINOCA compared to the group 2 patients with NSTE-ACS (1.35±0.37 mmol/l Trolox eq. vs. 1.46±0.28 mmol/l Trolox eq., p=0.036) (Fig.1).

Oxidative-reductive balance or REDOX index and oxidative profile of MINOCA patients were statistically higher compared to the patients with NSTE-ACS (72.04±7.4 vs. 54.86±20.6, p<0.0001 and 4.78±0.6 vs. 3.54±1.4, p<0.0001, respectively) (Fig.2).

FIGURE 2. The mean admission REDOX Index and Oxidative Profile in different groups of study patients



	MINOCA n=115	NSTE-ACS n=50	P value
REDOX Index, M±SD	72.04±7.4	54.86±20.6	**0.000**



	MINOCA n=115	NSTE-ACS n=50	P value
Oxidative Profile, M±SD	4.78±0.6	3.54±1.4	**0.000**

Abbreviations: REDOX index: oxidative-reductive balance; M±SD: mean ± standard deviation.

Admission inflammatory markers

The admission inflammatory markers such as high-sensitive C-reactive protein (hs-CRP) and lymphocyte-to-neutrophil ratio (NLR) were significantly higher in group 1 patients with MINOCA compared to group 2 patients with NSTE-ACS. (Tab.2)

TABLE 2. The mean admission hs-CRP and NLR in different groups of study patients

	MINOCA n=115	*NSTE-ACS n=50*	*P value*
hs-CRP, mg/dL, M±SD	1.87±0.66	1.54±0.35	**0.002**
NLR, M±SD	9.05±6.18	2.68±1.42	**0.000**

Abbreviations: hs-CRP: high-sensitive C-reactive protein; NLR: lymphocyte-to-neutrophil ratio; M±SD: mean ± standard deviation.

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DISCUSSION

Myocardial infarction with non-obstructive coronary arteries (MINOCA) occurs in a considerable proportion of cases fulfilling the diagnostic criteria for myocardial infarction (MI) with 3.5% 1-year mortality. [23,24]

According to the existing evidence, MINOCA patients are younger on average, with fewer comorbidities, and are predominantly female.[23-26]

In contrast of this, the percentage of female MINOCA patients in the present study was only 37% with an average age of 60, while the proportion of female patients in NSTE-ACS was 58% with an average age of 63 (p=0.011 for the female gender, and p=0.170 for age).

The growing evidence indicates the importance of oxidative stress and chronic inflammation in the heterogenous pathophysiology of MINOCA.[4-7] The inflammatory markers such as hs-CRP and hemogram-derived indices (NLR, etc.) are readily available in clinical practice, while the quantitative evaluation of high reactive species and antioxidant capacity in the clinical setting became possible during the last decade, thanks to the commercialization of technological achievements. Using one of these innovative methods, we have checked the free oxygen radical test (FORT) and free oxygen radicals defense (FORD) in patients with non-obstructive or obstructive coronary artery disease.

Despite of dramatic increase in free radical concentrations in both groups of study patients, there was no difference in the mean amount of overall organic radicals (FORT)(p=0.412). We also found a significantly lower mean concentration of plasmatic antioxidant compounds (FORD) in patients with MINOCA (p=0.036) compared with NSTE-ACS patients, indicating a more pronounced depletion of antioxidant potential in MINOCA patients.

Statistically significant differences in REDOX index and oxidative profiles, with a predominance of both in MINOCA patients, indicate the presence of progressive oxidative stress in this group of patients, compared with those with NSTE-ACS.

A statistically significant high REDOX index and oxidative profile in group 1 indicate more expanded oxidative stress in MINOCA patients compared with NSTE-ACS patients.

The results of admission inflammatory markers, such as hs-CRP and hemogram-derived NLR, suggest significantly higher inflammatory status in MINOCA patients than in those with NSTE-ACS.

Analyzing the limitations of the present study we found that it was single-center observational research with a limited sample size. We also did not differentiate patients with MINOCA type.

CONCLUSION

The results of the present study coincide with the accumulated evidence about the significance of oxidative stress and inflammation in the pathogenesis of MINOCA.

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