



Common and distinct changes of multi-marker panel in acute and chronic non-obstructive coronary syndromes

Mihaela Munteanu^{1*}

Abstract

Objective. Applying the multi-marker panel in patients with STEMI, NSTEMI and non-obstructive chronic coronary disease (no-CCD) aiming for the estimation of either common or non-common changes of admission levels of 37 markers.

Methods. The descriptive analytical study was conducted on 3 equal groups of patients (n=80 each) with STEMI, NSTEMI and no-CCD formed on the basis of a longitudinal cohort study comprising 516 patients with STEMI, 627 with NSTEMI and 173 patients with no-CCD. Serum levels of markers were determined by ELISA and cell flow cytometry.

Results. IL-1 β , soluble receptor of IL-6, TNF- α and hsCRP increased in all 3 groups, excepting normal level of neopterin and IL-10 inherent to no-CCD. Commonly for endothelial dysfunction was elevation of endocan and angiopoietin 2 (Apo2), whilst raising of endothelial microparticles characterized acute coronary syndrome (ACS). Decreased paraoxonase 1, Ang1-7/Ang II ratio and catestatin, as well as increased oxi-HDL, LP(a), Willebrand/ADAMTS13 ratio, neprilysin and growth differentiation factor 15 (GDF-15), are common signs as well.

Conclusion. Quite many similar changes of markers in patients with ACS and no-CCD suggest a pathogenic interface consisting of common pillars, which conceptually might also predict the coronary microcirculatory dysfunction often occurred in these pathologies.

Keywords

multi-marker panel, STEMI, NSTEMI, no-CCD

Introduction

The pathophysiological concept corroborates the evolution of ischemic cardiac disorders in a common scenario: atherosclerosis of the epicardial coronary arteries and arterioles of the microcirculatory system, augmented by inflammation, endothelial dysfunction, oxidative stress and the impact of various modifiable and non-modifiable cardiovascular risk factors (primarily age and gender), cardiovascular remodeling, endangerment of coronary reactivity to vasorelaxant and vasoconstrictor actions, neuroendocrine activation and pro-thrombotic status due to primary and secondary hemostasis impairment.

At the same time and in the presence of the same cardiovascular risk factors, some people develop acute coronary syndrome (ACS) manifested by the onset of acute myocardial infarction with either (STEMI) or without ST segment elevation (NSTEMI) caused by total or subtotal stenosis of the epicardial artery, and in others an ischemic anginal state develops being associated with an epicardial artery stenosis <50%, defined as non-obstructive chronic coronary disease (no-CCD), which has a much more favorable long-term forecast.

Unraveling the markers of these pathophysiological patterns using a multi-marker panel would underpin a justified algorithm for early and long-term prediction and, conversely, for consolidating therapeutic targets and optimizing individualized treatment.

Obviously, the feasibility of such a multi-marker panel and its predictive power is determined by the scientific acumen of the selection of circulating markers that must reflect the basic mechanisms of pathogenetic support of the events inherent to the ischemic status. In this regard, conceptual approaches guide preferentially towards: inflammation and endothelial dysfunction, oxidative stress and neuroendocrine activity, hemostasis, NETosis, atherogenicity and cardiovascular remodeling. To note that all explored markers (even new markers) have been used in different studies targeting the diagnostics and prediction of cardiovascular diseases.

Aim of study: To apply the multi-marker panel consisting of main classical and new markers reflecting mechanisms of cardiovascular events inherent to patients with STEMI, NSTEMI and no-CCD for underlying markers that can be used subsequently to create a prediction algorithm.

Methods

The descriptive analytical study was conducted on 3 equal groups of patients with STEMI (n=80), NSTEMI (n=80) and no-CCD (n=80), formed in a base of longitudinal cohort study comprising 516 patients with STEMI, 627 with NSTEMI and 173 patients with no-CCD aiming a reach of a conclusive homogeneity regarding age, gender and the presence of cardiovascular risk factors and comorbidities (table 1).

The diagnosis of these conditions included clinical data, ECG and coronary angiography. The study did not include patients with

*Corresponding author: Mihaela Munteanu; E-mail address: micaela.ivanov@gmail.com

¹Institute of Cardiology, Chişinău, Republic of Moldova

Table 1 - Indices of homogeneity of patient groups.

Index	STEMI	NSTEMI	no-CCD	p
Age (M±SD)	67.2±3,4	68.1±3,2	66.8±3,9	NS
Gender				
Male, n(%)	48(60)	43(53.7)	46(57.5)	NS
Female, n(%)	32(40)	37(47.3)	34(43.5)	NS
HTA, n(%)	71(88.7)	69(86.3)	73(91.2)	NS
DM, n(%)	26(32.5)	23(28.7)	25(31.2)	NS
Hypercholesterolemia, n(%)	56(70)	53(66.3)	59(73.7)	NS
Smoking, n(%)	14(17.5)	13(16.2)	18(22.5)	NS

Note: HTA – arterial hypertension; DM – diabetes mellitus; NS – no significant

Table 2 - Serum admission levels of inflammation markers (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
IL-1β, pg/ml	7.17±0.69	7.12±0.66	7.45±1.18	5.13±0.68
p vs control	<0.001	<0.001	<0.001	
IL-6, pg/ml	7.34±0.79	7.15±1.55	4.53±1.75	4.36±0.64
p vs control	<0.001	<0.001	=0.241	
IL-6-R, pg/ml	2.62±0.60	2.66±0.78	2.34±0.7	1.24±0.35
p vs control	<0.001	<0.001	<0.001	
IL-10, pg/ml	3.71±0.74	3.98±1.72	7.35±1.8	7.77±0.98
p vs control	<0.001	<0.001	=0.0529	
TNF-α, pg/ml	9.50±0.76	9.24±1.17	6.28±1.44	5.85±0.92
p vs control	<0.001	<0.001	=0.024	
Neopterin, nM/L	4.89±0.86	4.59±0.86	3.72±0.95	3.48±0.72
p vs control	<0.001	<0.001	0.0547	
hsPCR, mg/L	7.90±0.74	7.85±0.87	3.93±1.39	1.45±0.41
p vs control	<0.001	<0.001	<0.001	

acute and chronic inflammatory diseases, which could adversely affect the serum levels of markers. The control group consisted of 60 apparently healthy individuals. The serum content of 37 markers was determined by ELISA and cell flow cytometry methods summarized in following categories: (1) markers of inflammation, such as interleukin 1β (IL-1β), IL-6, soluble receptor of IL-6 (IL-6R), IL-10, tumor necrosis factor α (TNFα), high sensitivity C-reactive protein (hsCRP) and neopterin; (2) markers of endothelial dysfunction and re-endothelialization, such as endothelial microparticles (EMP, CD144+), endocan, nitric oxide (NO), angiopoietin-2 (Apo2) and endothelial progenitor cells (EPC); (3) markers of atherogenicity, such as lipoprotein a (Lp(a)), oxidized high density lipoprotein (oxi-HDL) and paraoxonase 1; (4) markers of oxidative stress, such as malonic dialdehyde (MDA), advanced oxidated protein products (AOPP), member of the NADPH oxidase (NOX-2); (5) markers of hemostasis, such as platelet microvesicles (PMV, CD62P), fibrine monomers (FM) and Willebrand/ADAMTS13 ratio; (6) markers of neuro-endocrine activity, such as neprilysin, adrenomedullin, Ang1-7/Ang II ratio, catestatin, NT-pro-BNP; (7) markers of neutrophile death (NETosis), such as myeloperoxidases (MPO), neutrophil elastases (NE), MMP-8 and E-selectin; (8) markers of cardiovascular remodeling, such as growth differentiation factor 15 (GDF-15), fibroblast growth factor 21 (FGF-21), transforming growth factor β (TGF-β), syndecan 1, galectine 3, MMP-2 and MMP-9. Serum marker levels were presented as mean and standard deviation (M±SD) and were normally distributed according to the Kolmogorov-Smirnov test. Statistical significance between control and study groups was

estimated using the two-tailed Student's t-test, value of p<0.05 being considered statistically significant.

Results

The inflammation response in study groups, compared to control, is presented in table 2.

In all 3 series of patients, the hsPCR level is more than 3 mg/L, which indicates a presence of high cardiovascular risk in either ACS or no-CCD. Regarding the intensity of inflammation to note the similar incremental rate of IL-1β and IL-6R in all series up to 98.5% vs control. However, IL-6 significantly increased only in ACS up to 68.3%. TNF-α exceeded control level in all patients, but neopterin, a marker of immune inflammation, is raised only in ACS. Thus, the inflammatory response is boosted in patients with ACS, which is consistent with the normal level of IL-10 in patients with no-CCD. Endothelial dysfunction is proper for all patients (table 3).

The level of EMP, a marker of endothelial injury, exceeded control only in ACS by up to 2.2 times. Endocan and Apo2 significantly increased in all 3 series of patients, whilst NO showed a common decline by 29-32%. Unlike ACS, feasibility of re-endothelialization is not altered in the no-CCD system, and the EPC level didn't differ from control.

According to marker results, oxidative stress is activated in all 3 series (table 4).

Table 3 - Serum levels of endothelial dysfunction and re-endothelialization markers (M±SD).

Marker	STEMI	NSTEMI	No-CCD	Control
EMP (CD144+), Nr./ml	328.09±37.58	282.97±59.86	158.44±55.69	148.58±10.46
p vs control	<0.001	<0.001	=0.0892	
Endocan, ng/ml	3.58±0.61	3.55±0.70	1.52±0.57	1.27±0.41
p vs control	<0.001	<0.001	=0.002	
NO, µM/L	50.65±7.77	52.66±0.78	51.49±11.27	74.21±8.47
p vs control	<0.001	<0.001	<0.001	
Apo 2, pg/ml	3289.6±350.3	3367.9±153.2	2719.6±396.7	2146.1±122.9
p vs control	<0.001	<0.001	<0.001	
EPC, Nr./µL	327.47±12.69	333.61±153.24	472.12±117.36	499.15±63.40
p vs control	<0.001	<0.001	=0.0543	

Table 4 - Serum admission levels of oxidative stress markers (M±SD).

Marker	STEMI	NSTEMI	No-CCD	Control
MAD, µmol/L	7.32±1.14	7.10±1.11	4.82±1.28	4.42±0.64
p vs control	<0.001	<0.001	=0.0136	
AOPP, µmol/L	71.91±14.26	70.77±13.98	50.26±7.15	41.83±4.53
p vs control	<0.001	<0.001	<0.001	
NOX-2, pg/ml	37.35±5.48	36.87±8.74	28.93±8.36	21.64±4.54
p vs control	<0.001	<0.001	<0.001	

Table 5 - Serum admission levels of atherogenicity markers (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
Paraoxonase 1, nM/mL	241.37±40.74	237.30±40.56	314.32±52.38	421.55±25.14
p vs control	<0.001	<0.001	<0.001	
LP(a), mg/dl	6.69±2.95	6.74±2.81	5.18±2.33	2.94±0.95
p vs control	<0.001	<0.001	<0.001	
oxi-HDL, u.c.	2.78±0.76	2.73±0.57	2.47±0.9	1±0.15
p vs control	<0.001	<0.001	<0.001	

Levels of MAD and AOPP were significantly elevated in no-CCD by 9-22%, and by over 65% in ACS. A reliable cause of oxidative stress activation is the increase of NOX-2: by 33.3% in no-CCD and by over 76% in ACS. Inflammation, oxidative stress and compromised re-endothelialization are in a mutual relationship with atherogenicity, the main markers of which could be reliable predictors of coronary incompetence (table 5).

Remarkably, the significant increase in serum oxi-HDL level happened in all groups up to 178%. A putative causative factor of oxi-HDL excess would be the decline of paraoxonase-1 by 25% in no-CCD, and by 32-34% in ACS. Also important in this sense is the elevation of circulating LP(a) levels by 76.2% in no-CCD and by over 127.5% in STEMI and NSTEMI as well.

A common disorder of hemostasis for all patients is raising of von Willebrand/ADAMTS13 ratio by 50% in no-CCD, and by 85.7-120.6% in ACS. However, the FM and PMV levels significantly increased only in ACS (table 6).

Noteworthy, specific markers of NETosis are not changed in no-CCD. In contrary, ACS is associated with significant elevation of all explored markers: MMP-8 by 89.2%; NE by 100% and MPO by 113-155%. NETosis boosting in ACS correlates with an increased level of E-selectin (neutrophil chemokine) by over 48% (table 7).

A factor that is ubiquitous in myocardial ischemia is neuroendocrine activation that has an important pathogenetic contribution to coronary incompetence and remodeling, as well as distant repercussions. Our study identified this phenomenon, revealing the key traits (table 8).

First of all, it is worth mentioning the significant increase in neprilysin levels in all patients: by 91.8% in no-CCD and by over 300% in ACS. This is conceptually matched with the reduction in the Ang1-7/Ang II ratio by 22-30%, given the ability of this protease to cleave Ang 1-7. The basic marker of heart failure, NT-pro-BNP, is only increased in patients with ACS: by 183% in STEMI and by 262% in NSTEMI.

Another marker, adrenomedullin, reflecting circulatory dyshomeostasis and stress-induced activation of vascular endotheliocytes, is significantly increased in all groups by up to 66.7%. Common for all groups regarding neuroendocrine activation is the reduced level of catestatin. Diminution of this marker is similar in ACS and no-CCD, with a decline level attested in a range of 54-63%.

Myocardial ischemia triggers the remodeling of the coronary system (both epicardial arteries and microcirculation arterioles), the myocardium, and the extracellular matrix. This will adversely influence the prognosis of ischemic diseases. The analysis of the 7

Table 6 - Serum admission levels of hemostasis markers (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
PMV, CD62P, 1/ μ L	319.08±84.19	304.94±92.03	175.46±67.77	161.37±16.85
p vs control	<0.001	<0.001	=0.059	
FM, mg/ml	8.41±1.03	8.42±2.07	4.75±0.94	4.54±0.63
p vs control	<0.001	<0.001	=0.0716	
vWillebrand/ ADAMTS13, u.c.	2.78±1.46	2.34±0.92	1.89±0.59	1.26±0.38
p vs control	<0.001	<0.001	<0.001	

Table 7 - Serum admission levels of specific markers of NETosis (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
MMP-8, ng/ml	53.62±6.53	52.57±6.53	30.78±9.08	28.81±6.45
p vs control	<0.001	<0.001	=0.0767	
NE, ng/ml	31.56±4.71	32.82±9.21	17.63±6.09	16.16±4.14
p vs control	<0.001	<0.001	=0.0553	
MPO, U/ml	74.84±11.61	62.83±13.94	31.34±9.2	29.25±5.87
p vs control	<0.001	<0.001	>0.05	
E-selectin, ng/ml	95.07±4.71	101.31±14.95	71.14±11.73	64.36±7.93
p vs control	<0.001	<0.001	=0.0791	

Table 8 - Serum admission levels of neuroendocrine activity markers (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
Nephrilysin, ng/ml	1.99±0.82	2.07±0.67	0.94±0.36	0.49±0.38
p vs control	<0.001	<0.001	<0.001	
Ang 1-7/Ang II, u.c.	0.62±0.25	0.67±0.44	0.69±0.55	0.88±0.064
p vs control	<0.001	<0.001	=0.0053	
NT-pro-BNP, pg/ml	402.74±182.80	514.12±99.01	151.23±45.16	142.44±17.25
p vs control	<0.001	<0.001	>0.05	
Adrenomedullin, pg/ml	32.11±5.92	30.78±5.53	20.55±4.68	12.82±2.99
p vs control	<0.001	<0.001	<0.001	
Catestatin, ng/ml	0.83±0.69	0.81±0.75	0.85±0.27	1.75±0.34
p vs control	<0.001	<0.001	<0.001	

Table 9 - Serum admission levels of cardiovascular remodeling markers (M±SD).

Marker	STEMI	NSTEMI	no-CCD	Control
GDF-15, ng/ml	2.67±0.81	2.86±0.82	2.45±0.75	1.29±0.44
p vs control	<0.001	<0.001	<0.001	
FGF-21, pg/ml	92.21±9.94	91.66±11.54	66.36±8.09	64.29±6.39
p vs control	<0.001	<0.001	=0.0532	
TGF- β , ng/ml	8.15±1.13	7.31±1.12	5.11±1.36	4.85±0.87
p vs control	<0.001	<0.001	=0.1	
Syndecan 1, ng/ml	261.50±36.17	246.74±36.17	128.25±15.81	125.86±7.39
p vs control	<0.001	<0.001	=0.0601	
Galectine-3, ng/ml	7.66±1.78	6.71±2.01	3.81±1.28	3.52±0.78
p vs control	<0.001	<0.001	=0.05789	
MMP-2, ng/ml	4.92±1.30	4.61±1.42	3.81±1.28	25.17±0.77
p vs control	<0.001	<0.001	=0.0511	
MMP-9, ng/ml	21.73±3.79	22.56±4.86	16.35±7.87	14.71±2.64
p vs control	<0.001	<0.001	=0.0614	

markers that are accepted for assessing cardiovascular remodeling shows some important particularities regarding ACS and no-CCD (table 9).

The level of GDF-15 is comparable and significantly increased in all patients, by up to 122%. However, two other growth factors, such as FGF-21 and TGF- β , significantly increased only in ACS.

The increase of TGF- β levels by up to 68% is associated with an almost twofold increase in serum content of syndecan 1, a membrane receptor of this growth factor. Moreover, the increase of syndecan 1 in ACS is matched by an increase in the circulating level of metalloproteinases, MMP-2 and MMP-9, which cleave the TGF- β receptor expressed on different cells. Galectin-3, the

marker of interstitial remodeling, was also found to be significantly increased only in patients with ACS. So, only GDF-15, as a marker of cardiovascular remodeling, is significantly elevated in all studied patients with either ACS or no-CCD.

Discussion

In this descriptive analytical study, we aimed to evaluate the multi-marker panel consisting of 37 classical and new markers determined in serum at admission in three series of patients with STEMI (n=80), NSTEMI (n=80) and no-CCD (n=80) having a conclusive homogeneity regarding age, gender, incidence of cardiovascular risk factors and comorbidities. The assessed markers reflect main mechanisms of coronary diseases, such as inflammation, endothelial dysfunction, re-endothelialization, atherogenicity, oxidative stress, hemostasis, NETosis, neuroendocrine activity and cardiovascular remodeling. The basic goal of this approach was to disentangle through a comparative exegesis the common and distinct marker changes in patients with ACS and no-CCD, which can subsequently be used as a tool to establish a reliable prediction algorithm. Likewise, in regard to the role of coronary microcirculation dysfunction (CMD) in ischemic myocardium evolution we tried in a conceptual field to propose markers which can plausibly be attributed to CMD [1, 2, 3].

Inflammation, endothelial dysfunction, oxidative stress and pro-thrombotic hemostasis have, according to marker assessment, a higher intensity in patients with ACS vs no-CCD. The unraveled common and distinct changes of markers could gain an important pathophysiologic support facilitating the prediction of major cardiovascular events (MACE) risk. Thus, IL-1 β and IL-6R were significantly elevated versus control and had similar values in patients with ACS and no-CCD. However, in patients with no-CCD, there was no increase of IL-6 and neopterin, possibly due to the normal level of IL-10, which is able to mitigate inflammation response. Enhanced neopterin in ACS indicates the activity of immune assisted inflammation, and this marker is also proven as a prediction of congestive heart failure [4]. In a previous study, we demonstrated the high predictive value of neopterin regarding the risk of MACE at a 1-year follow-up period of post-infarction evolution in patients with STEMI and NSTEMI [5].

With reference to endothelial dysfunction, it should be noted that the decreased NO level is common for ACS and no-CCD. Elevated levels of endothelial microparticles are characteristic of patients with STEMI and NSTEMI, corresponding to a weak capacity of re-endothelialization due to a lowered number of endothelial progenitor cells. Decreased re-endothelialization is found in an intelligible connection with angiopoietin 2 raising, which jeopardizes the insertion of EPC in the zone of coronary endothelial injury. Importantly, in patients with no-CCD a significant elevation of endocan is established, although much below the incremental value of the marker detected in patients with ACS. So, it might be appreciated as a predictor of endothelial dysfunction, even in the presence of normal EPC levels [6].

The diagnostic and predictive value of endocan in patients with STEMI and NSTEMI, as well as with heart failure and essential

arterial hypertension, is also reported by other authors [7, 8, 9]. Our data also outline the predictive feasibility of endocan in patients with no-CCD regarding endothelial dysfunction, inclusively targeting coronary microcirculation. The TNF- α elevation in no-CCD is also reported by other authors [10], which justifies including this marker in the diagnostic and prognostic algorithm.

Markers of oxidative stress and atherogenicity are significantly deviated from control in all 3 groups of patients. Remarkably, the increased level of oxi-HDL is similar in patients with ACS and no-CCD, which correlates with the decline of paraoxonase 1, an enzyme that controls in an inhibitory manner the process of HDL molecule oxidation. Collectively, these markers could be used in early prediction of atherosclerosis boosting risk as well as in an early initiation of anti-atherogenic treatment. N. Pagonas et al (2020) also found an elevation of oxi-HDL in patients with coronary ischemic diseases [11].

Hemostasis markers have shown a notable activation of primary and secondary hemostasis in patients with ACS based on the elevation of FM, PMV, as well as the Willebrand/ADAMTS13 ratio. In a previous study, we demonstrated the predictive value of FM and the Willebrand/ADAMTS13 ratio on the risk of MACE in patients with NSTEMI [12]. The last marker also significantly increased in patients with no-CCD, hence indicating the pathogenetic contribution of the primary hemostasis. So done, this new marker may open new perspectives in the prediction of the microthrombotic pattern of coronary microcirculation dysfunction.

NETosis is not boosted in patients with no-CCD, accompanied by a weak change in E-selectin level. In contrary, NETosis is a powerful tool in myocardial injury in patients with STEMI and NSTEMI [13].

Regarding neuroendocrine activity, it is worth noting the double decrease of catestatin levels in all groups of patients. This oligopeptide inhibits the release of catecholamines, resulting in the activation of the sympatho-adrenergic system, which was associated with a significant decrease of Ang 1-7/Ang II ratio. This decline is matched by neprilysin rise, a zinc-dependent metalloprotease which cleaves a lot of peptides, including those that have a vasorelaxant effect, such as Ang1-7, bradykinin, natriuretic peptide C, etc. In our study, neprilysin is significantly above the control value, the incremental value being practically equal in all series, thus approaching neprilysin as a therapeutic target.

Likewise, it is important to underline the double enhancement of GDF-15 in all groups of patients. The conceptual interest concerning GDF-15 derives from the publication of R. Tian et al (2024), who uphold its predictive value of coronary microcirculation dysfunction in patients with STEMI [14]. CMD is found in 30-50% of patients with STEMI and NSTEMI, a phenomenon that detrimentally influences the post-infarction clinical evolution as well as the risk of MACE. The elevation of GDF-15 in patients with no-CCD can be empirically accepted as a prediction of CMD, which represents the pathophysiological support of the imminent patterns, such as ANOCA, INOCA, MINOCA [15, 16].

Finally, our data have a tight adherence to the conceptual pillars of coronary dysfunction pathophysiology analyzed in an integrative interface by using a multi-marker panel [16, 17, 18].

Conclusion

Quite many similar changes of markers in patients with ACS and no-CCD suggest a pathogenic interface consisting of common pillars, which conceptually underline especially the role of inflammation, endothelial dysfunction, hemostasis disorder and neuroendocrine activity. Likewise, a few markers should be highlighted in order to be included in a follow-up study aiming to outline a predictive algorithm of coronary events, such as IL-1b, endocan, Willebrand/ADAMTS3 ratio, Ang1-7/Ang II ratio, paraoxonase 1, catestatine, HDL-oxi and GDF-15.

Acknowledgments

To the Polyvalent Hospital “Nova-Med” for helping in the STEMI patient research.

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Funding

There was no funding for this work.

Conflicts of interest

None declared.

Informed Consent Statement

Written informed consent has been obtained from the patients to publish this paper.