

Endocan: a biomarker predicting successful reperfusion after coronary artery by-pass surgery of acute coronary syndrome patients

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Abstract. – OBJECTIVE: Endothelial specific molecule 1 (Endocan) is a biomarker of the inflammatory process occurring in endothelial cells. It was shown that endocan was increased in acute coronary syndromes. We aimed at investigating the endocan levels in acute coronary syndrome patients after coronary bypass surgery.

PATIENTS AND METHODS: The study included 35 patients who presented with acute coronary syndrome to the Emergency Department. Serum endocan levels and other inflammatory markers were evaluated before and after coronary artery by-pass surgery. The correlation coefficients and their significance were calculated by Pearson's test and the difference in mean values before and after bypass surgery was calculated by paired sample *t*-test. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was taken as $p < 0.05$.

RESULTS: There was a significant change in serum hs-CRP and endocan levels and also LVEF before and after CABG operation ($p < 0.05$).

CONCLUSIONS: Serum endocan level was significantly decreased after successful reperfusion in our study. Thus, it may be an important biomarker in terms of clinical use as an indicator of successful reperfusion.

Key Words

Endocan, CABG, Reperfusion, Acute coronary syndrome.

nary syndromes. However, there is no study about how the endocan level is affected after a successful reperfusion in acute coronary syndromes. We aimed at investigating the endocan levels in acute coronary syndrome patients after coronary by-pass surgery.

Patients and Methods

Study Design

This case-control study was carried out in the Internal Medicine Inpatient Clinics of Bahcesehir University Medical Faculty Hospital. Approval was obtained from the Medical Research Ethics Committee of Bahcesehir University Medical Faculty. It was conducted in accordance with the Ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All of the subjects provided written informed consent.

Patients Selection

This cross-sectional study was performed at Bahcesehir University Medical Faculty, Istanbul, Turkey. Approval for the study was obtained from the Medical Research Ethics Committee of Bahcesehir University Medical Faculty. The study included 35 patients who presented to the Bahcesehir University Medical Faculty Emergency Department and were diagnosed as having ACS. Inclusion criteria were patients aged more than 18 years who were undergoing diagnostic coronary angiography for ACS, characterized by the presence of chest pain or ischemic equivalent at rest, lasting longer than 20 minutes associated with one of the following conditions: ECG showing ST segment elevation or depression ≥ 1.0 mm in two or more contiguous leads; elevated biomarkers of myocardial necrosis (i.e. CK-MB > 1 time the upper limit of normal of the local laboratory, or hs-Troponin T ≥ 14 pg/ml). Exclusion criteria

Introduction

Endothelial specific molecule 1 (Endocan) is a biomarker of inflammatory process occurring in endothelial cells^{1,2}. It has shown that it is increasing not only in atherosclerosis, coronary artery diseases, hypertension and diabetes mellitus, but also in the other inflammatory processes such as cancers, vasculitis and infection diseases²⁻⁷. It was shown that⁶ endocan was increased in acute coro-

were: myocardial ischemia precipitated by a condition other than atherosclerotic coronary artery disease (e.g. arrhythmia, severe anemia, hypoxia, thyrotoxicosis, cocaine, severe valvular disease, hypotension); coronary stent placement within the last 30 days; severe chronic kidney disease with measured or calculated glomerular filtration rate using Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD4) formula of < 30 ml/min/1.73 m², or renal dialysis; inflammatory diseases and/or malignancies in activity. During the study, the patients' age, sex and risk factors for ACS were recorded, in addition to the results of the physical examination, ECG, hs-Troponin T levels, complete blood counts, basic blood biochemical parameters, diagnostic coronary angiograms.

Coronary Angiography Analysis and Revascularization Decision

Diagnostic coronary angiographies were performed in all patients after admission using standard techniques with a femoral approach. The severity of CAD was assessed by two experienced independent observers using Syntax scoring system; they were blinded to both the patient's clinical characteristics. Revascularization decision was taken by a heart team.

Serum Endocan Measurements

In order to estimate the serum levels of endocan, 10 ml of peripheral venous blood were drawn within 24 hours of admission and after 72 hours of bypass surgery, into plain blood collection tubes without any additives, and immediately immersed in melting ice and allowed to clot for one hour before centrifugation (1700 g at 4°C for 10 minutes). Serum was stored at -80°C until analyzed, and samples were thawed only once. Endocan levels were measured using an enzyme-linked immunosorbent assay (Endocan ELISA kit, Eastbiopharm Co., Hangzhou, China). Measurements of cardiac enzymes and other biochemical parameters were performed using standard laboratory techniques in all subjects.

Statistical Analysis

Continuous variables with parametric distribution were expressed as mean±standard deviation. Categorical data were expressed as frequencies and their differences were analyzed using the Chi-square test. Serum endocan levels and other variables were investigated using visual (histo-

grams, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. Parameters who were normally distributed, the correlation coefficients, and their significance, were calculated by Pearson's test and the difference in mean values before and after bypass surgery was calculated by paired sample *t*-test. A 5% type I error level was used to infer statistical significance. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., IBM, Armonk, NY, USA). Statistical significance was taken as $p < 0.05$.

Results

Study Population, Baseline Clinical And Laboratory Findings

A total of 35 patients were enrolled into the study. The clinical and laboratory characteristics of the study population are shown in Table I. The mean age was 62.4 ± 11.1 and male gender was dominant with a rate of 77%. Medications at admission and the distribution of coronary artery risk factors such as diabetes mellitus, hypertension, hyperlipidemia, smoking and family history of coronary artery disease are also shown in Table I.

Table I. Baseline characteristics of the study group .

Variables	Mean±Std. Deviation or n (%)
Age (year)	62.4 + 11.1
Male [n (%)]	27 (77)
Hypertension [n (%)]	15 (43)
Diabetes mellitus [n (%)]	16 (46)
Hyperlipidemia [n (%)]	17 (49)
Smoking [n (%)]	13 (37)
Family History of CAD	19 (54)
LVEF (%)	49.5 + 7.5
LDL (mg/dl)	157.1 + 66.7
Hs-troponin (pg/ml)	2738 + 7042
Total cholesterol (mg/dl)	195.7 + 38.5
HbA1C (%)	7.3+1.6
Fasting glucose (mg/dl)	121 + 37
GFR (mL/min/1.73 m ²)	80 + 16.9
Medications [n (%)]	
• ACEi/ARB	13 (37)
• B Blockers	16 (46)
• CCB	8 (23)
• Antiplatelet	12 (34)
• Statins	10 (28)

Inflammatory Biomarkers and Ejection Fraction Change after Revascularization With Coronary Artery By-Pass Graft Operation

Inflammatory markers such as hs-CRP and endocan before coronary artery by-pass graft operation (CABG) were shown as hs-CRP_b and endocan_b in Table II-III. Left ventricle ejection fraction of the study group before CABG was shown as LVEF_b. These parameters were shown as hs-CRP_a, endocan_a and LVEF_a after CABG operation. There was a significant change in serum hs-CRP and endocan levels and also LVEF before and after CABG operation (Figure 1). The mean levels of hs-CRP and endocan before CABG operation were 37.5 and 372.8, respectively. The mean levels of hs-CRP and endocan after CABG operation were 12.3 and 320.2, respectively. The *p*-values were 0.001 and 0.003, respectively. The mean LVEF before and after CABG operation was 49.4% and 51%, respectively. The *p*-value of the difference in LVEF before and after CABG operation was 0.035. There were statistically significant difference in hs-CRP, endocan and LVEF levels before and after CABG (Table II and III).

Discussion

The aim of this study was to investigate the change in endocan levels after reperfusion via coronary artery bypass surgery in patients with

acute coronary syndrome. In our study, there was a statistically significant decrease in endocan levels after surgical reperfusion. Our study is the first clinical study that shows a significant reduction in serum endocan levels after successful reperfusion in acute coronary syndrome patients. Inflammation plays an important role in the occurrence of acute coronary syndrome. Inflammatory cells, proteins, and responses from vascular cells play a central role in the pathogenesis of different stages of acute coronary syndrome, including the initiation and progression of atheroma, plaque instability, and rupture⁸. Initial step of vascular inflammation leading to atherosclerosis is the adhesion that involves the rolling, tethering, adherence, and migration of leukocytes through the endothelium. Enrollment and accumulation of leukocytes to the endothelium is an end of up-regulation of adhesion molecules⁹. Endocan, which is a dermatan sulfate proteoglycan, is expressed in endothelial cells and also can be measured in serum. It is accepted as a potential endothelial cell marker and plays a significant role in endothelial-dependent pathologic diseases such as inflammatory disorders, adhesion, migration and angiogenesis¹⁰. The expression of endocan is regulated by several cytokines and growth factors. TNF-alpha and IL-1 have been shown to induce endocan expression *in vitro*. Endocan is a potential cardiovascular risk⁸ but the exact roles of endocan for cardiovascular risk in patients with coronary artery disease have not been explained satisfactorily. Yilmaz

Table II. Paired samples test for serum Endocan levels, hs-CRP levels and ejection fractions values before and after revascularization.

Pairs	Mean	Std. Deviation	95% Confidence Interval of the Difference	<i>p</i>-value
hsCRP _b -hsCRP _a (mg/L)	25.15	36.82	4.04	0.001
Endocan _b -Endocan _a (ng/ml)	52.6	97.46	3.19	0.003
EF _b -EF _a (%)	-1.5	3.99	-2.21	0.035

Table III. Paired samples test for serum Endocan levels, hs-CRP levels and ejection fractions values before and after revascularization.

Pairs	Mean	Std. Deviation	<i>p</i>-value
Pair 1	hsCRP _b (mg/L)	37.5	44.028
	hsCRP _a (mg/L)	12.34	12.734
Pair 2	Endocan _b (ng/ml)	372.83	366.698
	Endocan _a (ng/ml)	320.23	319.786
Pair 3	EF _b (%)	49.47	7.539
	EF _a (%)	51.03	7.76

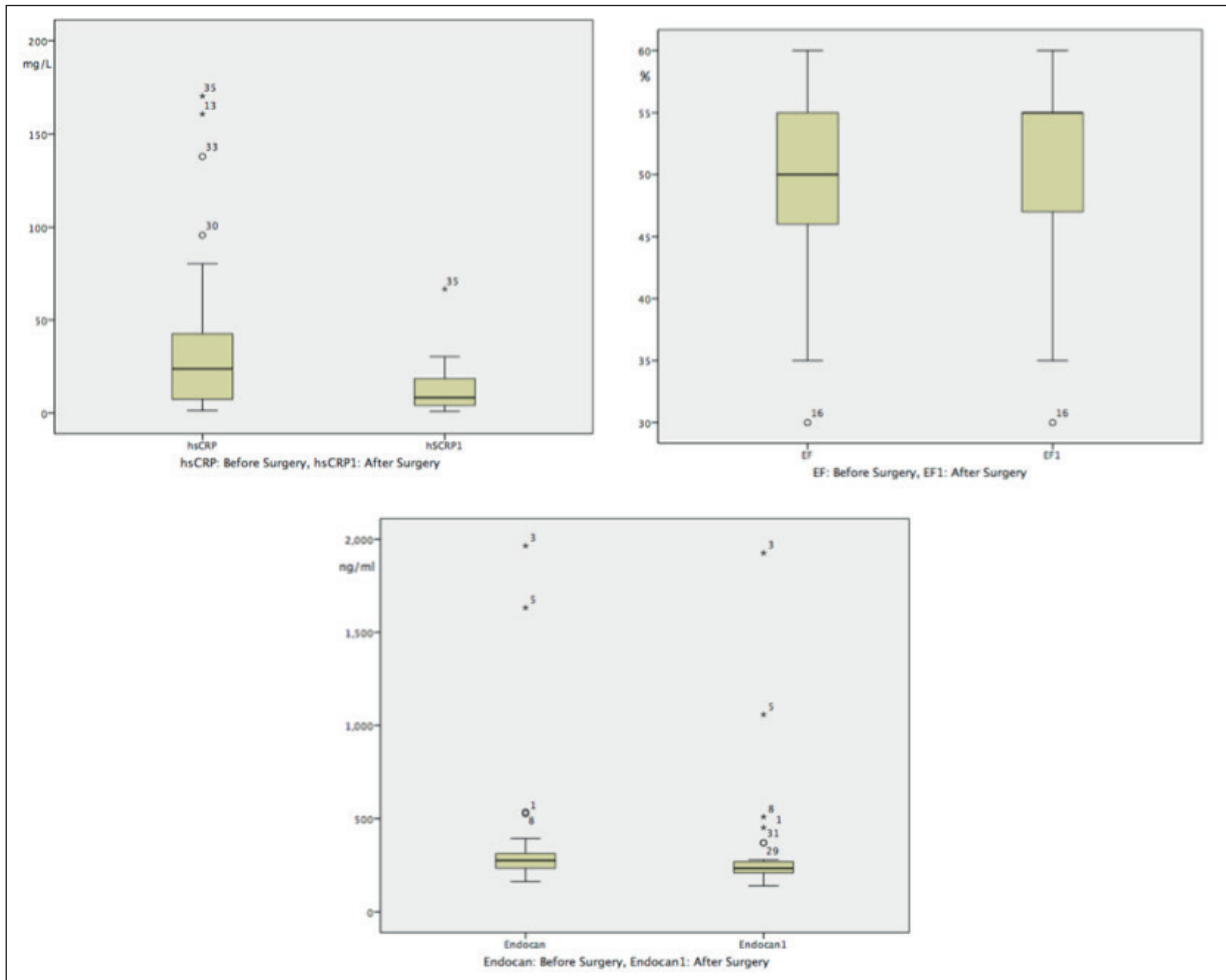


Figure 1. The change in serum hs-CRP, endocan levels and also LVEF before and after CABG operation is shown in Figure 1.

et al¹¹ also determined that plasma endocan levels correlated positively with both markers of inflammation, and were associated with all-cause mortality and cardiovascular incidents in patients with chronic kidney diseases (CKD). Therefore, plasma endocan levels increase in the presence of decreasing GFR and effect all-cause mortality and cardiovascular incidents in patients with CKD, independent of traditional and nontraditional risk factors. In the light of this study, one of the exclusion criteria of our study was chronic kidney disease, as it is an independent cause of high serum endocan levels. Previous studies have shown a significant increase in serum endocan levels in many diseases such as chronic atherosclerotic events, acute coronary syndrome, endothelial injury, hypertension and diabetes^{1,6-8}. However, it was not clear whether this increase was a result of primary disease or a result of increased

endocan levels. Glycemic regulation plays an important role in cardiovascular risk in patients with diabetes mellitus (DM). Elevated levels of endocan in patients with poor glycemic regulation and significant reduction in endocan levels after 3 months of DM treatment was demonstrated in a previous study⁷. Also, in a pilot study, Balta et al¹ showed that endocan levels were higher in newly diagnosed patients with hypertension compared with normotensive patients, and endocan levels correlated with carotid intima-media thickness and high-sensitivity CRP. Celik et al¹¹ assessed the effect of amlodipine vs. valsartan on endocan levels in patients newly diagnosed with hypertension. Both amlodipine and valsartan were associated with a significant decrease in endocan and high sensitivity-CRP levels. Also in our study, we have demonstrated significant decrease in endocan and high sensitivity-CRP levels after suc-

successful reperfusion with coronary artery by-pass surgery. This study has some limitations: firstly, it is a cross-sectional study and patient population is relatively small. Secondly, as there is no clarity in terms of timing of endocan measurement, a follow-up of serum endocan levels during the hospitalization will be more valuable.

Conclusions

We found that serum endocan level was significantly decreased after successful reperfusion in our study. Thus, it may be an important biomarker in terms of clinical use as an indicator of successful reperfusion. Prospective and long-term endocan monitoring with larger patient populations will provide further guidance.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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