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The Role of Interleukin-1 and Interleukin-6 in the Development of Acute Myocardial Infarction

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Abstract

Certain cytokines as interleukin-1 (IL-1) and interleukin-6 (IL-6) are produced by the neutrophils and macrophages localized in the atheromatous plaques. The levels of circulating inflammatory cytokines IL-1 and IL-6 are found to be significantly increased in patients with ST-Segment Elevation Acute Myocardial Infarction (STEMI).

In a group of 38 patients with STEMI, the levels of IL-1ß and IL-6 were determined in the coronary circulation (CC) by analysis of aspirates from the culprit lesions and the levels of these inflammatory markers in the systemic (peripheral) circulation (SC) during STEMI and six months after STEMI. Coronary angiography (CA) and percutaneous coronary intervention (PCI) were performed in all patients and the levels of cytokines were determined by the ELISA method. By examining the levels of IL-1ß and IL-6, the aim of this study was to determine their predictive value in short-term prognosis.

In the acute phase (STEMI) there was a statistically significant difference between the mean values of IL-1ß (p=0, 000000) and IL-6 (p=0, 026204) in the samples of CC and SC, respectively. Results from the six months of follow-up showed that there were statistically no significant differences between the mean values of IL-1ß and IL-6 in the CC and SC. Moderate and low-positive correlation between the mean values of IL-1ß (r=0,6816; p=0,000) and IL-6 (r=0,4291; p=0,000) in CC and SC was observed at the sixth month of follow-up.

In conclusion, our results confirm that IL-1ß and IL-6 are linked to the progression of Coronary Artery Disease (CAD) and should be considered as predictive markers.

Keywords: Acute myocardial infarction, Coronary artery disease, Cytokines, ST Elevation Myocardial Infarction, Interleukins.

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1. Introduction

Acute ischemic attacks are connected to atherosclerotic lesions in the blood vessels. An erosion or rupture of vulnerable lesions can cause atherothrombotic complications like acute myocardial infarction, stroke, renal failure, heart failure, sudden death and peripheral artery disease (Cohn et al., 2004; Hansson, 2005). ST-segment elevation myocardial infarction (STEMI) arises form an occlusion of the coronary artery leading to an acute manifestation of heart attack with a risk of serious complications and death since it is a total vessel blockage.

Plasma lipids (cholesterol and triglycerides) as well as lipoproteins play important role in pathogenesis of atherosclerosis since growing of the lesion composed of lipids was accepted to be a primary cause for lumen occlusion which leads to occurrence of ischemic heart and cerebrovascular events (Ross et al., 1976; Harker et al., 1976; Kannel et al.,1979; Martin et al.,1986; Lloyd-Jones et al., 2001). However, coronary artery disease can be found in high percentage of population with clinically not evident dyslipidemia (Braunwald,1997). Aside the significant risk factors as smoking and arterial hypertension, the occurrence of atherosclerosis is very complex and its pathogenesis includes dyslipidemia, endothelial dysfunction and inflammation (Libby,2002; Willerson et al., 2004; Szmitko et al, 2003; Hansson et al., 2005).

Endothelial dysfunction is defined as a failure of the endothelium to produce endogenic vasodilating molecule of nitrogen monoxide (NO) (Ko et al., 2002). Combined with the formation of atherosclerotic plaques, the endothelial dysfunction plays important role in pathophysiologic processes in the blood vessels (Szmitko et al., 2003). This molecule creates antithrombotic environment by limitation of the platelet aggregation on the endothelium, by prevention of leucocyte adhesion on the endothelium via suppression of the adhesion molecules` expression and by keeping vascular smooth muscle cells (VSMC) in non-proliferative condition. Vascular smooth muscle cells constitute the center layer of arteries wall called tunica media, respond to stimuli by contracting and therefore regulate the systemic blood pressure (de Graaf et al., 1992; Gauthier et al., 1995; Cornwell et al., 1994).

The atherosclerotic vascular disease remains a cause for significant morbidity, mortality and financial costs in the World, besides the advances in the prevention and treatment. It is a chronic inflammatory process which includes several cell types as monocytes/macrophages, dendritic cells, lymphocytes, endothelial cells and VMSC in different stadiums of activation, apoptosis and necrosis. The processes in the above-mentioned cells are initiated and managed by a complex network of factors called cytokines. Inflammatory and resident vascular cells produce and recognize cytokines allowing interaction between these two systems (Cohn et al., 2004; Hansson, 2005). Understanding the function of these cytokines and their effects on cells in the atherosclerotic plaques may largely contribute to discovering targets for therapeutic intervention.

The family of IL-1 consists of 4 proteins: IL-1α., IL-1ß, IL-1 receptor antagonist and IL-18. IL-1 is mainly produced by macrophages but also neutrophils, lymphocytes, dendritic cells, endothelial cells, hepatic cells, fibroblasts and muscle cells. Main target for IL-1 are cells of the immune system, like monocytes, lymphocytes and granulocytes. IL-1 plays a central role in the

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cytokine network and processes in the cardiovascular system, including cytokine proliferation, regulation of the cell growth, contractility or apoptosis of the cardiovascular cells and activation of the leucocytes and platelets. IL-1ß is produced by monocytes, macrophages, endothelial cells and VMSC. It is stimulated by pro-inflammatory factors as TNF-α. (Venugopal et al., 2002). IL-6 has pro- and anti-inflammatory features. It is produced not only by the immune cells including monocytes and macrophages, but also by endothelial cells and VMSC (Lindmark et al., 2001). IL-6 is involved in stimulation of B-cell differentiation, lymphocyte activation and T-cell differentiation, as well as macrophage and natural killer (NK) cells activation (Ross et al., 1999).

The aim of this study was to determine the levels of IL-1ß and IL-6 in the coronary and systemic (peripheral) circulation during STEMI and six months after STEMI. Furthermore, the aim was to compare the levels of these inflammatory markers obtained by analysis of the aspirates of the culprit lesions with the levels of inflammatory markers obtained from systemic circulation during STEMI and six months after STEMI, and to determine their predictive value in short-term prognosis of the examined patients.

2. Methods

In this study, 38 patients with STEMI attending the University Clinic of Cardiology were included, after being selected according the inclusion and exclusion criteria. The STEMI was defined as chest pain at rest, associated with ST-segment elevation in at least 2 consecutive leads with cut-off value of 2 mm (0,2 mV). Patients were recruited using the following inclusion criteria: ST-segment elevation myocardial infarction with elevation of the ST-segment of at least 2.0 mm or more; chest pain onset within last 12 hours; and age between 20 and 60 years. Exclusion criteria were: patients with autoimmune disorders; febrile patients during the intervention; STEMI with duration of more than 12 hours; patients with STEMI with indication for CABG; and patients with acute or subacute stent thrombosis during initial PCI procedure. Patients with autoimmune disorders were excluded because of altered cytokine levels, which could influence the study's results. The patients revisited the Clinic every month after STEMI for routine control and on the sixth month a re-coronarography was made.

Coronary angiographies (CA) and percutaneous coronary interventions (PCI) were performed on all patients according to the standard protocols as follows. After preparing the access site for approach, usually the groin for the femoral artery, an introducer needle is inserted in the artery. A guidewire is passed, and the needle is withdrawn. Once the access is gained, a "sheath introducer" is inserted over the guidewire, which helps to keep the artery open. A sheath is then inserted through the sheath introducer. The sheaths are flexible hollow tubes used to introduce different catheters. Different types of catheters are used to access different locations like right and left coronary arteries and left ventricle. With X-ray fluoroscopy, contrast material is introduced in the coronary artery to delineate its anatomy. Stenosis or occlusion of the coronary artery is then visualized, and severity is estimated through pictures at different angles. If stenosis or occlusion is located, the cardiologist then introduces a guidewire through the catheter and positions the tip of the wire distal to the stenosis in the artery. This guidewire is then used to introduce the balloon or stent catheter over it for angioplasty or stent placement, respectively.

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For stent placement, the catheter has the stent positioned over the balloon, and once in the right location, the balloon can be expanded, which stretches the stent open over the balloon. The catheter can then be withdrawn. Images are taken to confirm the proper location of the stent and resolution of stenosis (Lawton et al., 2022).

In our patients, at least one culprit lesion during coronary angiography was expected to be determined. A culprit lesion is defined as a lesion which causes occlusion (100%) or sub-occlusion (99% stenosis) of the coronary artery, onset of chest pain and can be confirmed by the presence of thrombus by angiography.

All percutaneous procedures were performed by radial (trans radial) approach according to Seldinger technique. After detection of the culprit lesion, patients were pretreated with unfractionated heparin of 100 IU/kg. The culprit artery was intubated with 6F or 7F guiding catheter using diagnostic guidewire and standard 0.014" coronary wire through the culprit lesion till the end of the artery was used.

The thrombus aspiration technique involved Export thrombus aspiration catheter (Medtronic®) which was engaged to the coronary wire. Proximal end of the thrombus aspiration catheter is connected to the vacuum-syringe, while distal tip has a hole which serves for aspiration of the thrombotic material. During opening of the vacuum-syringe, the thrombus was removed from each coronary artery by simple mechanic aspiration technique and the aspirates from the culprit lesions were collected.

Then, PCI procedure with or without balloon pre-dilation and implantation of one or more stents was performed. Patients were closely monitored for occurrence of future cardiovascular events like cardiovascular death, myocardial infarction, newly diagnosed angina and repeated revascularization procedure. Follow-up of the patient was at 1, 3 and 6 months after performing primary PCI.

Blood samples from systemic circulation were provided by collecting blood from the radial artery whereas blood samples from coronary circulation (culprit lesion) were provided by collecting aspirates from the culprit coronary vessel by thrombus aspiration technique as previously explained. Collected blood samples with anticoagulant (EDTA) were centrifuged on 1500 G and the obtained plasma samples were stored on -80^{o}C.The levels of IL-1ß and IL-6 in coronary and systemic circulation during STEMI and six months after STEMI were determined by ELISA method using commercially available tests from eBiosciences, Affimetrix, USA (Human IL-1β Platinum ELISA, Human IL-6 Platinum ELISA).

Statistical analysis was performed by using XLSTAT 2016. The Kolmogorov-Smirnov test was used to evaluate the distribution of the biochemical parameters. The Wilcoxon signed-rank test was used to compare the levels of inflammatory markers (IL-1β and IL-6) in the systemic and coronary circulation. Comparison between the two examined groups was performed by using Mann-Whitney test while Friedman test was used for multiple comparisons among the examined groups. Values for $p<0.05$ were considered statistically significant.

3. Results

From the 38 patients in this study, 34 (89.5%) were male and 4 (10.5%) females. Mean age of the patients was 51.1±9.4 years. Almost 74% of patients had arterial hypertension, 60.5% had dyslipidemia, 18.4% had diabetes mellitus and 68.4% of them were smokers. Concerning localization of acute myocardial infarction (AMI), 42.1% of patients had inferior wall AMI, 52.6% had anterior wall AMI and the rest 5.3% had lateral wall AMI. In 52.5% of patients, the culprit artery was the left anterior descending artery (LAD), in 39.5% was the right coronary artery (RCA) and in 7.9% it was the obtuse marginal branch (OM). We observed lethal outcome of 7.9% in the six months of follow-up period.

Mean value of IL-1ß from the blood samples of peripheral circulation in patients with STEMI (acute phase) was 1.8±0.7, with minimal value 1.3 and maximal value 4.24. Values obtained from coronary circulation were higher, with mean value of 3.2±1.04, minimal 1.39 and maximal value 5.01. Mean value of IL-6 in blood samples of peripheral circulation in patients with STEMI (acute phase) was 5.6±6.3, with minimal 0.29 and maximal value 31.1. Values obtained from coronary circulation were higher, with mean value of 14.9±25.8, minimal 0.5 and maximal value 144.2. Six months after STEMI, the mean value of IL-1ß in blood samples of peripheral circulation was 2.2±0.8, with minimal value 0.22 and maximal value 4.9. Values obtained from coronary circulation were higher, with mean value of 2.4±0.9, minimal 1.02 and maximal value 5.04. Mean value of IL-6 in blood samples of peripheral circulation was 3.7±3.9, with minimal 1.13 and maximal value 19.5. Values obtained from coronary circulation were higher, with mean value of 4.1±4.5, minimal 1.58 and maximal value 26.63(Table 1).

Table 1. Values of inflammatory markers (IL-1ß, IL-6) in blood samples from peripheral and coronary circulation in acute phase (STEMI) and 6 months after STEMI.

		Parameter	Valid N	Mean	Minimum	Maximum	Std.Dev.
Acute phase (STEMI)	Peripheral circulation	IL-1ß	38	1.83105	1.3	4.24	0.71385
		IL-6	38	5.60763	0.29	31.13	6.25902
	Coronary circulation	IL- 1ß	38	3.17447	1.39	5.01	1.04634
		IL-6	38	14.88789	0.5	144.2	25.81322
6 months after STEMI	Peripheral circulation	IL-1ß	35	2.20114	0.22	4.9	0.76243
		IL-6	35	3.68371	1.13	19.49	3.89559
	Coronary circulation	IL- 1ß	35	2.36714	1.02	5.04	0.93439
		IL-6	35	4.07886	1.58	26.63	4.51393

The Mann-Whitney U test showed statistically significant difference between mean values of IL-1ß in blood samples of peripheral and coronary circulation in acute phase (STEMI). The difference between mean values in this phase of IL-6 in blood samples of peripheral and coronary circulation was also statistically significant. The Mann-Whitney U test showed statistically no significant difference between mean values of IL-1ß in blood samples of peripheral and coronary circulation six months after STEMI. The difference between mean values of IL-6 in blood samples of peripheral and coronary circulation was also statistically no significant (Table 2).

Table 2. Levels of inflammatory markers (IL-1ß, IL-6) in blood samples of peripheral and coronary circulation in acute phase (STEMI) and 6 months after STEMI.

	Parameter	Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
Acute phase (STEMI)	IL-1ß	927.500	1998.500	186.5000	-5.56315	0.00000
	IL-6	1249.000	1677.000	508.0000	-2.22318	0.02620
6 months after STEMI	IL-1ß	1207.000	1278.000	577.0000	-0.41699	0.67668
	IL-6	1145.000	1340.000	515.0000	-1.14524	0.25210

Low positive correlation of IL-6 in blood samples of peripheral and coronary circulation in acute phase (r=0.4822, p=0.002) and low negative correlation of IL-1ß in blood samples of peripheral and coronary circulation in acute phase (r=-0.3626, p=0.025) were observed. In the phase of six months after STEMI, moderately positive correlation of IL-1ß and low positive correlation of IL-6 between blood samples of peripheral and coronary circulation with p=0.000 was found (Table 3).

Table 3. Correlation of IL-1ß and IL-6 between blood samples of peripheral and systemic circulation 6 months after STEMI (p=0.000).

Parameter	r	p
IL-1ß	0.6816	0.000
IL-6	0.4291	0.000

The difference between mean values of IL-1ß in blood samples of peripheral circulation in acute phase (STEMI) vs. 6 months after STEMI was statistically significant (p=0.000004). The difference between mean values of IL-1ß and IL-6 in blood samples of coronary circulation in acute phase (STEMI) vs. 6 months after STEMI was statistically significant (p=0.016174 and p= 0.019148. respectively) (Table 4).

Table 4. Values of IL-1ß and IL-6 in blood samples of peripheral and coronary circulation in acute phase (STEMI) and 6 months after STEMI

	Parameter	Rank Sum Group 1	Rank Sum Group 2	U	Z	p-level
Peripheral circulation	IL-1ß	1016.500	1909.500	275.5000	-4.63856	0.000004
	IL-6	1581.000	1345.000	604.0000	1.22587	0.220249
Coronary circulation	IL-1ß	1694.500	1231.500	490.5000	2.40499	0.016174
	IL-6	1688.500	1237.500	496.5000	2.34265	0.019148

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Low positive correlation of IL-1ß levels in blood samples of peripheral circulation in acute phase (STEMI) and 6 months after STEMI with p=0.028 was determined. Furthermore, a statistically no significant correlation of IL-1ß and IL-6 levels between blood samples of coronary circulation in acute phase (STEMI) and 6 months after STEMI was observed (Table 5).

Table 5. Correlation of IL-1ß and IL-6 levels between blood samples of peripheral circulation in acute phase (STEMI) and 6 months after STEMI and between blood samples of coronary circulation in acute phase (STEMI) and 6 months after STEMI.

	Parameter	r	p
Peripheral circulation	IL-1ß	0.3708	0.028
	IL-6	-0.1699	0.329
Coronary circulation	IL-1ß	-0.0537	0.759
	IL-6	-0.1628	0.350

4. Discussion

Inflammatory cells and cytokines contribute to the development of atherosclerotic lesions. Cytokines like TNF-α or IL-1 stimulate expression of IL-6 and IL-8 in neutrophils and macrophages located in the atherosclerotic plaques. Besides the vascular origin, these cytokines can also be increased and reflect general inflammatory processes like chronic infections or processes associated with atherogenesis and its clinical manifestations. In patients with AMI there are significantly higher levels of inflammatory cytokines IL-1, IL-6 or TNF-α and IL-1 receptor antagonist. (Henrichot et al, 2005).

Our study revealed statistically significant difference between mean values of IL-1ß and IL-6 in blood samples of peripheral and coronary circulation in acute phase (STEMI) and statistically no significant difference between mean values of IL-1ß and IL-6 in blood samples of peripheral and coronary circulation six months after STEMI. The difference between mean values of IL-1ß and IL-6 in blood samples of coronary circulation in acute phase (STEMI) vs. 6 months after STEMI was statistically significant. The time of 6 months after STEMI for comparison of IL-1ß and IL-6 was chosen according to literature data and in line with the expectations for alterations in their levels per certain time.

The previous research has shown that IL-1 is one of the most important mediators of the inflammatory response which induces the cascade of pro-inflammatory molecules. Thus, IL-1 is part of the pathogenesis of cardiovascular diseases (Banda et al., 2005).Since IL-1ß initiates expression of other cytokines in several cellular types it also has a pro-inflammatory effect by itself. Primary cytokines (TNF-α, IL-1) stimulate production of endothelial cells, adhesive molecules, pro-coagulants and other mediators present in circulation, but also stimulate production of IL-6 which induces expression of hepatic genes leading to activation of the circulating reactants of the acute phase, like CRP (Ross et al., 1999; Lindmark et al., 2001).IL-6 is a

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central mediator of acute phase response and primary determinant of the hepatic production of CRP (Momiyama et al., 2005).

IL-1ß has a very important role in early phase of the lesion formation. It stimulates the leucocyte extravasation in the developing lesion and cytokine expression in almost every single cell present in the lesion. It is proven that IL-1ß increases expression of the tissue factor and induces pro-coagulant activity. Certain IL-1ß gene polymorphisms may be associated with occurrence of acute myocardial infarction in early ages, most probably due to activated coagulation caused by inflammation (Henrichot et al., 2005; Iacoviello et al., 2005).

The pro-atherosclerotic effects of IL-1ß have been shown in animal model studies. Infusion of fake IL-1 receptor reduced lipid plaque in ApoE-/- mice. Enlarged region of the lesion has been observed in IL-1 receptor/ApoE-/- double knockout mice and double knockout mice IL-1ß/ApoE showed 30% reduction of atherosclerosis (Lee et al., 2005).

IL-6 is signalized via JAK/STAT family of signal transductors and is mitogenic for VSMC. IL-6 accelerates expression of cell adhesion molecules (CAM) on endothelial cells and VSMC thus contributing towards extravasation of leucocytes in developing atherosclerotic lesion. In patients with acute coronary syndrome, leucocyte adhesion is increased contributing to strong inflammatory response. IL-6 is expressed on the human atherosclerotic plaque and it is increased in serum of the patients with CAD and unstable angina. Therefore, it is considered as an independent risk factor for CAD (López-Cuenca et al., 2013).In FRISC II study, IL-6 was independent predictor of mortality in patients with AMI (FRISC II, 1999).

A study on 212 STEMI patients treated with percutaneous coronary intervention (PCI), examined eight inflammatory cytokine levels in corelation with possibility of a major adverse cardiac event risk. The results indicated that TNF-α, IL-8, IL-17A, and VCAM-1 levels were elevated in STEMI patients compared to angina pectoris patients, while IL-1β, IL-6, IL-10, and ICAM-1 were of no difference, concluding that IL-17A and VCAM-1 can be correlated with increased risk of major adverse cardiac event in STEMI patients (Zhang et al., 2022). However, in a similar study on 41 patients with STEMI who underwent primary PCI, 6 months follow up showed that 20.5% presented signs of LVR, and 24.4% had MACE. The plasmatic levels of IL-6, IL-1RA and resistin were all significantly associated with LVR and MACE in these patients, indicating them as good predictors both as independent variables and also as a group for development of such events (Scărlătescu et al., 2022).In a study conducted on Javanese populations, the GG genotype of the IL-6 G174C SNP was predominant suggesting that studies on different IL-6 loci or haplotype in population should be conducted in connection with Atherosclerotic Cardiovascular Disease and Cardiovascular Mortality Risk Scores(Susilo et al., 2022).

The results presented in our study are in line with other such studies and confirm the potential of IL-1ß and IL-6 as biomarkers. Drugs as Tocilizumab for IL-6, or Anakinra as an IL-1 receptor antagonist have been recently tested in terms of development and progression prevention of atherosclerosis (Tsioufis et al., 2022). Su at al. conclude that anti-IL-6-related drugs or inhibitors

have a therapeutic prospect (Su et al., 2021). The further step would be to employ cytokine-targeted treatment of atherosclerotic disease if to be proven beneficial.

5. Conclusion

The levels of the two analyzed inflammatory cytokines IL-1ß and IL-6 were higher with statistical significance in coronary versus peripheral circulation in acute phase (STEMI). A statistically significant positive correlation of the levels of IL-1ß and IL-6 in peripheral and coronary circulation in the phase of six months after STEMI was detected. The levels of IL-1ß in blood samples from peripheral circulation were significantly increased six months after STEMI event. According to the presented results, a correlation between the levels of IL-1ß and IL-6 and the progression of CAD was determined, suggesting the use of these cytokines as predictive markers.

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References

Banda NK, Guthridge C, Sheppard D, et al. Intracellular IL-1 receptor antagonist type 1 inhibits IL-1-induced cytokine production in keratinocytes through binding to the third component of the COP9 signalosome. *J Immunol*. 2005; 174: 3608-3616. DOI: 10.4049/jimmunol.174.6.3608

Braunwald E. Shattuck lecture--cardiovascular medicine at the turn of the millennium: triumphs. concerns. and opportunities.*N Engl J Med*. 1997;337(19):1360-9.DOI: 10.1056/NEJM199711063371906

Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA. Surrogate markers for cardiovascular disease: functional markers.*Circulation*. 2004;109(25 Suppl 1): IV31-46. DOI: 10.1161/01.CIR.0000133442.99186.39

Cornwell TL, Soff GA, Traynor AE, Lincoln TM Regulation of the expression of cyclic GMP-dependent protein kinase by cell density in vascular smooth muscle cells. *J VascRes*. 1994;31(6):330-7.DOI: 10.1159/000159061

de Graaf J, Demacker PN. Stalenhoef AF. LDL oxidation and coronary atherosclerosis. *Lancet*. 1992; 340(8811):123-4. DOI: 10.1016/0140-6736(92)90453-a

FRISC II investigators. FRagmin and Fast Revascularization during Instability in Coronary artery disease. *Lancet*. 1999; 354:701-707. DOI:10.1016/S0140-6736(99)07350-X

Gauthier TW, Scalia R, Murohara T, Guo JP, Lefer AM. Nitric oxide protects against leukocyte-endothelium interactions in the early stages of hypercholesterolemia. *ArteriosclerThrombVasc Biol*. 1995;15(10):1652-9. DOI: 10.1161/01.atv.15.10.1652

Hansson GK, Edfeldt K, Toll to be paid at the gateway to the vessel wall. *ArteriosclerThrombVasc Biol*. 2005;25(6):1085-7.DOI: 10.1161/01.ATV.0000168894.43759.47

Hansson GK. Inflammation. atherosclerosis. and coronary artery disease. *N Engl J Med*. 2005; 352(16):1685-95.DOI: 10.1056/NEJMra043430

Harker LA, Ross R, Slichter SJ, Scott CR.Homocystine-induced arteriosclerosis. The role of endothelial cell injury and platelet response in its genesis. *J Clin Invest.* 1976 ;58(3):731-41.DOI: 10.1172/JCI108520

Henrichot E, Juge-aubry CE, Pernin A et al. Production of chemokines by perivascular adipose tissue: a role in the pathogenesis of atherosclerosis? *ArterioscIerThrombVasc Biol*. 2005; 25: 2594-2599. DOI: 10.1161/01.ATV.0000188508.40052.35

Iacoviello L, Di Castelnuovo A, Gattone M, et al. Polymorphisms of the interleukin-1beta gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro. *ArterioscIerThrombVasc Biol.*2005; 25: 222-227.DOI: 10.1161/01.ATV.0000150039.60906.02

Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study.*Ann Intern Med*. 1979;90(1):85-91.DOI: 10.7326/0003-4819-90-1-85

Ko L, Maitland A, Fedak PWet al. Endothelin blockade potentiates endothelial protective effects of ACE inhibitors in saphenous veins. *Ann Thorac Surg*. 2002;73(4):1185-8. DOI: 10.1016/s0003-4975(01)03605-0

Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(3):e4-e17. DOI:10.1161/CIR.0000000000001039

Lee KW, Lip GY, Tayebjee M, Foster W, Blann AD.Circulating endothelial cells. von Willebrand factor. interleukin 6 and prognosis in patients with acute coronary syndromes. *Blood*. 2005;105(2):526-32.DOI: 10.1182/blood-2004-03-1106

Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868-74.DOI: 10.1038/nature01323

Lindmark E, Diderholm E, Wallentin L, Siegbahn A. Relationship between interleukin 6 and mortality in patients with unstable coronary artery disease: effects of an early invasive or noninvasive strategy. *JAMA*. 2001; 286: 2107–2113.DOI: 10.1001/jama.286.17.2107

Lloyd-Jones DM, O'Donnell CJ, D'Agostino RB, Massaro J, Silbershatz H, Wilson PW. Applicability of cholesterol-lowering primary prevention trials to a general population: the framingham heart study.*Arch Intern Med*. 2001;161(7):949-54.DOI: 10.1001/archinte.161.7.949

López-Cuenca A, Manzano-Fernández S, Lip GY et al.Interleukin-6 and High-sensitivity C-reactive Protein for the Prediction of Outcomes in Non-ST-segment Elevation Acute Coronary Syndromes.*Rev EspCardiol*. 2013; 66(3):185-92.DOI: 10.1016/j.rec.2012.07.019

Martin NA, Hadley MN, Spetzler RF. Carter LP. Management of asymptomatic carotid atherosclerosis.*Neurosurgery*. 1986;18(4):505-13.DOI: 10.1227/00006123-198604000-00026

Momiyama Y, Ohmori R, Ohsuzu F. Association between IL-1beta gene polymorphism and myocardial infarction. *ArteriosclerThrombVasc Biol*. 2005; 25: 36. DOI: 10.1161/01.ATV.0000159700.18731.d2

Ross R. Atherosclerosis-an inflammatory disease. *N Engl J Med*. 1999; 340: 115–126.DOI: 10.1056/NEJM199901143400207

Ross R. Harker L. Hyperlipidemia and atherosclerosis.*Science*. 1976; 193(4258): 1094-100.DOI: 10.1126/science.822515

Scărlătescu AI, Micheu MM, Popa-Fotea N et al. IL-6, IL-1RA and Resistin as Predictors of Left Ventricular Remodelling and Major Adverse Cardiac Events in Patients with Acute ST Elevation Myocardial Infarction. *Diagnostics*. 2022 ;12(2):266. DOI: 10.3390/diagnostics12020266

Su JH, Luo MY, Liang N et al. Interleukin-6: A Novel Target for Cardio-Cerebrovascular Diseases. *Front Pharmacol*. 2021; 12: 745061. DOI: 10.3389/fphar.2021.745061

Susilo H, Thaha M, Pikir BS et al. The Role of Plasma Interleukin-6 Levels on Atherosclerotic Cardiovascular Disease and Cardiovascular Mortality Risk Scores in Javanese Patients with Chronic Kidney Disease. *J Pers Med*. 2022; 12(7):1122. DOI: 10.3390/jpm12071122

Szmitko PE, Wang CH, Weisel RD, de Almeida JR, Anderson TJ, Verma S. New markers of inflammation and endothelial cell activation: Part I. *Circulation*. 2003;108(16):1917-23.DOI: 10.1161/01.CIR.0000089190.95415.9F

Szmitko PE, Wang CH, Weisel RD, Jeffries GA, Anderson TJ, Verma S. Biomarkers of vascular disease linking inflammation to endothelial activation: Part II. *Circulation*. 2003;108(17):2041-8.DOI: 10.1161/01.CIR.0000089093.75585.98

Tsioufis P, Tsioufis K, Tousoulis D. The Impact of Cytokines in Coronary Atherosclerotic Plaque: Current Therapeutic Approaches. *Intern J Mol Sci*. 2022; 23(24):15937. DOI: 10.3390/ijms232415937

Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation*. 2002; 106:1439–1441. DOI: 10.1161/01.cir.0000033116.22237.f9

Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor.*Circulation*. 2004;109(21 Suppl 1): II2-10.DOI: 10.1161/01.CIR.0000129535.04194.38

Zhang J, Xu H, Yao M, Jia H, Cong H. The abnormal level and prognostic potency of multiple inflammatory cytokines in PCI-treated STEMI patients. *J Clin Lab Anal*. 2022; 36:e24730. DOI: 10.1002/jcla.24730