INFLUENCE OF INSULIN-LIKE GROWTH FACTOR-I LEVELS ON THE COURSE OF ACUTE MYOCARDIAL INFARCTION

Kapustnik V.[1], Martovytskyi D.[1], Shelest B.[1], Shelest O.[1], Ponomarenko F.[2]

[1] Kharkiv National Medical University, Ukraine
[2] Municipal non-profit enterprise "City Polyclinic No. 11" of Kharkiv City Council, Ukraine

https://doi.org/10.35339/ic.8.4.211-216

Abstract

Over the recent years, cardiovascular disease has reached epidemic proportions among chronic noncommunicable diseases worldwide. According to the latest tendencies, cardiovascular diseases play the leading role in formation of current negative health and demographic trends in Ukraine and all over the world: they significantly affect the main health indicators: morbidity, mortality, disability, life expectancy and quality of life. The recent 20 years, are characterized by triplication of the prevalence of CVDs among the Ukrainian population, the mortality rate from them has risen by 40%. This review analyzes serum level of insulin-like growth factor-I (IGF-I) in patients with acute myocardial infarction and his role in left ventricular remodelling. The scientific data regarding the neurohumoral component of acute myocardial infarction pathogenesis have been expanded by increasing levels of the angiogenesis marker IGF-I, which can be explained by his properties as markers of the acute phase of inflammation. An analysis of the relationship between troponin I and IGF-I, a marker of myocardial damage, showed a direct relationship, indicating an increase in troponin I concentration with rising serum IGF-I levels. This indicates that the activity of the angiogenesis marker IGF-I may be associated with the severity and depth of myocardial damage.

Keywords: *coronary heart disease, acute myocardial infarction, cardio markers, insulin-like growth factor-I.*

BACKGROUND

Among the many forms of coronary heart disease (CHD) today, the most life-threatening is acute myocardial infarction (AMI) [1-4]. According to various sources, every year more than 16 million new cases of AMI are recorded in the world, and its consequences can be observed in a few days or in months and years. According to the American Heart Association, within six years of undergoing AMI, 18% of men and 35% of women have a recurrence of AMI, and 22% of men and 46% of women become disabled due to severe chronic heart failure. 30-40% of patients have left ventricular dysfunction [5].

Preventive focus of modern cardiology is the search for fundamentally new risk factors and early diagnosis and prognosis of cardiovascular disease [6-8]. Thus, protein growth factors and damage in acute coronary syndrome were identified: pregnancy-associate IGF-I plays an important d plasma protein-A (PAPP-A) and IGF-I. PAPP-A and IGF-I are protein complexes circulating in the blood, the increase in the concentration of which in CHD indicates the instability of atherosclerotic plaques [9, 10].

The purpose of the review was to highlight the effect of the serum level of insulin-like growth factor-I on the pathogenetic features of endothelial dysfunction in patients with acute myocardial infarction.

Association of IGF-I serum levels with acute myocardial infarction

IGF-I is a protein from the family of insulin-like growth factors, similar in structure and function to insulin. It helps to repair damaged tissues, stimulate neoangiogenesis and vasodilation. It is synthesized mainly by the liver and kidneys, but also by the paracrine and autocrine pathways, vascular endothelial and smooth muscle cells, and cardiac myocytes [11, 12].

PAPP-A is a zinc-containing matrix metalloproteinase secreted by fibroblasts when atherosclerotic plaque is damaged.

Corresponding Author:
Dmytro Volodymyrovych Martovytskyi, PhD, Department of Internal and occupational diseases, Kharkiv National Medical University, Ukraine.
E-mail: dv.martovytskyi@knmu.edu.ua

The molecular structure of IGF-I is very similar to the structure of insulin. IGF-I plays an important role in cell survival and growth by binding to a specific receptor (IGF1R), which is present in many cell types, including cardiac myocytes. IGF1R receptor activation has been shown to reduce apoptotic and necrotic cell death induced by ischemia as well as reperfusion injury by stimulating the intracellular phosphoinositide 3-kinase, protein kinase B and extracellular signaling-regulated signaling pathway [13-15].

Researchers such as Buerke M et al. [16] administered IGF-I 1 hour before rat myocardial ischemia for 20 minutes, followed by reperfusion. IGF-I maintained the state of ischemic myocardium due to inhibition of cardiac necrosis by polymorphonuclear-induced leukocytes and inhibition of reperfusion apoptosis of cardiac myocytes.

Davani EY et al. [17] caused isolated ischemia in the rat myocardium for 20 minutes, followed by reperfusion for 2 hours with a modified Krebs cycle or Krebs cycle with the addition of IGF-I. IGF-I, administered immediately after reperfusion, protected the ischemic myocardium from further injury through mitochondrial-dependent mechanisms that support the mitochondrial-to-nDNA ratio within the heart tissue.

Interventions are also known, O'Sullivan JF et al. [18], which caused ischemia/reperfusion in pigs by balloon occlusion of the middle left anterior descending coronary artery for 90 minutes, followed by reperfusion for 2 hours. After 2 hours of reperfusion, IGF-I was delivered to the ischemia via the intracoronary route. Thirty minutes after IGF-I treatment, it caused an increase in IGF-I receptor activation, as well as protein kinase B activation and glycogen synthase kinase-3, which are signaling pathways for IGF-I receptor activation.

Within 24 hours after IGF-I treatment, the apoptosis of cardiomyocytes in the area of myocardial infarction was significantly reduced compared to pigs that were not treated with IGF-I. Two months after IGF-I treatment, myocardial infarction decreased, myocardial collagen, and decreased fibrotic markers decreased; increase in the number of cardiomyocytes in the area of infarction; improved movement of the walls of the left ventricle; global reperfusion and left ventricular function have improved.

Padin-Iruegas ME et al. [19] suggested that the mechanism of cardioprotective effects of IGF-I was due to the activation of receptors for IGF-I, which flow into the caspase pathways. Another key-note conclusion of the mentioned work is the presence of defensive features of IGF-I, even when it was administered relatively late after reperfusion.

Other researchers who have studied myocardial ischemia [20] have suggested that if reperfusion injury exists, the window for improving myocardial reperfusion may be much wider than previously thought. Evidence that low doses of IGF-I reduced necrosis and at least partially reduced apoptosis suggests that apoptosis by reperfusion may result in significantly greater cardiac cell death than previously thought. This finding also raises the question of whether early administration of IGF-I (during or within minutes of reperfusion) would lead to an even greater degree of improvement in the affected myocardium.

It is known that exogenous IGF-I increases myocardial contractility in the short and long term [21-23]. In healthy subjects, IGF-I increases insulin sensitivity and increases plasma glucose loss and tissue glucose utilization [24]. Thus, significant data suggest a possible cardioprotective role of IGF-I.

According to another study, patients with a favorable course of acute myocardial infarction had significantly lower concentrations of IGF-I compared with those with an unfavorable course. One year later, IGF-I values returned to normal [25, 26].

Another study [27] found that low IGF-I levels in patients with CHD were associated with mortality over the next two years. Since there was no control group in this study [27], it cannot be compared with ours. Another previous study [28] of 122 people who underwent coronary angiography reported a significant reduction in IGF-I in patients with significant CHD (126±7 ng/ml) compared to people without it.

It is also unclear whether a marked decrease in IGF-I is a primary change or a secondary phenomenon for myocardial necrosis and associated neurohumoral environment [29, 30]. Given the physiological half-life of IGF-I circulating within 10 hours [31], a reduction in the risk of recurrence of myocardial infarction in patients seems unlikely. Neurohumoral changes following myocardial infarction, including elevated

cortisol, interleukin-1, and tumor necrosis factor-alpha (which inhibit IGF-I release) [32] or reduce IGF-I-binding proteins (which may prolong plasma half-life IGF-I) [33, 34], possibly would help reduce IGF-I. This is evidenced by the inverse relationship between IGF-I levels and the delay that separates the sample from the onset of symptoms.

In 2010, Japanese researchers published the results of a genetic study of case-control studies involving 320 patients with myocardial infarction and 307 healthy volunteers: they found proportions of IGF-I genes that probably differ in groups [35]. This study demonstrates that the specific nucleotide sequence of the IGF-I gene can be used as a genetic marker of high risk of myocardial infarction.

In recent years, there have been quite a few studies examining the IGF-I participation in the coronary atherosclerosis evolving in patients without pituitary disease. The first clinical study involving 218 individuals, which found a probable decrease in IGF-I levels in patients with myocardial infarction, was conducted in 1997 [36]. An inverse relationship between IGF-I and the risk of CHD and its complications, including cardiovascular mortality, as well as stroke, has been found in other, later studies [37]. It is also known that low levels of IGF-I correlate with the length of the QT interval regardless of heart rate, which indicates its effect on repolarization in the myocardium and the likelihood of developing threatening ventricular arrhythmias [38]. But there are also opposite data: people with high levels of IGF-I are more likely to develop CHD [39].

IGF-I as a marker of the acute phase of inflammation in AMI

The presence of AMI is followed through a growth in the level of IGF-I, which may be due to its properties as a marker of the acute phase of inflammation. Thus, according to several studies, IGF-I levels correlate with the risk of cardiovascular disease in the general population [40, 41]. It has been reported that low levels of IGF-I may be an independent risk factor for myocardial infarction and CHD, as well as prevent obesity, insulin resistance, impaired glucose intolerance [42]. According to Andrade D et al., (2020) Increased IGF-I activity is associated with cavity hypertrophy and myocardial wall thickening, as well as increased inotropic heart function, and increased IGF-I levels after AMI have been associated with increased PV and myocardial hypertrophy [43].

As it can be seen, some studies [44, 45] have shown an association between a known marker of myocardial damage, troponin I, and a marker of IGF-I angiogenesis, which also allows us to consider it as a marker of acute inflammation in AMI.

Conclusions

The numerous works demonstrate that IGF-I, a new highly sensitive biochemical marker of vascular inflammation and damage, can be used in the laboratory diagnosis of acute coronary syndrome in patients with and without obesity. In the aspect of the "cardiovascular continuum", the reparative role of IGF-I is systemic, having a beneficial effect on the kidneys, nevertheless, the pathogenetic, prognostic and therapeutic effects of IGF-I in patients with AMI requires further investigation.

Declarations

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

Funding Sources

There are no external sources of funding

Data Transparency

The data can be requested from the authors.

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Received: 03-Oct-2021
Accepted: 13-Dec-2021