Regionally Influenced Content of Selenium and Its Capacity under Postoperative Myocardial Remodeling in Cardiac Surgery Patients

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Abstract. Selenium (Se) is an essential micronutrient in living organisms; however, some aspects of its metabolism and function remain unknown. Se deficiency causes significant disturbances in the cardiovascular system along with left ventricular (LV) fibrosis. Simultaneously, an understanding of pathways that influence Se role in heart failure progression is insufficient. Therefore, clinical studies are needed to characterize Se importance in developing post-infarct LV dysfunction and postoperative remodeling. In the Tomsk region, the level of Se in healthy people and the myocardium of patients with ischemic cardiomyopathy was close to normal. Quantitative chemical analysis of Se content in hair samples and LV myocardium was based on stripping voltammetry to determine mass concentrations of the micro-element. Nevertheless, a significant number of cardiac surgery patients showed negative dynamics of postoperative LV myocardium remodeling with the development of heart failure. We obtained preliminary results of a direct correlation between favorable outcomes of postoperative adaptive myocardial remodeling (AR) and maladaptive myocardial remodeling (MALR) with different Se concentrations in the myocardium. Simultaneously, about 84% of patients showed abnormal postoperative LV MALR in high Se in the myocardium. Further in-depth studies are required to translate novel data from the laboratory bench to the clinics.

Keywords: Selenium · Hair · Healthy volunteers · Myocardium · Stripping voltammetry · Ischemic cardiomyopathy · Postoperative left ventricular remodeling

1. Introduction

It is estimated that an additional 3 million people will develop heart failure (HF) by 2030, representing a 25% increase in prevalence relative to 2010 [2]. Ischemic heart disease plays a significant role (up to 60% of cases) in the development of HF that, in 10–35% of cases, subsequently leads to ischemic cardiomyopathy (ICMP). ICMP manifests itself in cardiomegaly (dilated “heart remodeling”) and clinical symptoms of a left ventricular insufficiency [8]. Surgical intervention is often the only way to manage HF, but some patients develop repeated LV remodeling and postoperative deterioration [7]. The etiology and pathogenesis of repeated remodeling remain unknown. The relationship between selenium intake and various health outcomes, particularly cardiomyopathy and myocardial ischemia/reperfusion injury, is discussed [1]. One of the most common causes of ICMP in endemic Se deficient areas is a Keshan disease (KD). Hair analysis is considered an acceptable right way for Se content estimation [11]. Early studies have shown a low Se content in the Hair of both men and women in the Tomsk region and
a progressive decrease in its concentration in patients with cancer of the digestive tract [4]. This paper presents the results of Se content analysis in relatively healthy residents of Tomsk and cardiac surgery patients with ICMP after postoperative LV remodeling.

2. Materials and Methods

The examination of 74 healthy volunteers and 159 cardiac patients was approved by the Ethics Committee (certificate No. 583 of March 19, 2007) of the Siberian State Medical University (Tomsk). The subjects have informed about the features of the conducted diagnostic procedures underper ethical requirements. The Hair of healthy volunteers with a thickness of 2–3 mm² was cut off at 3–5 points. The total volume of the hair sample was about 100 mg. LV myocardium (0.5 mm³) biopsy samples were taken intraoperatively. LV autopsy samples were taken during the post-mortem examination of both sexes with no cardiovascular pathology due to an acute injury.

Quantitative chemical analysis of hair and myocardium samples for selenium content was based on stripping voltammetry to determine the deficient trace element's low concentrations, as described previously [5]. The detection of the trace element in each patient was performed in triplets. Before the study, 10 cm³ of the background electrolyte solution was introduced into a quartz glass with a capacity of 15–25 cm³ using a pipette. At the electrolysis potential, \( E_e = -(0.8 \pm 0.1) \) V accumulation was carried out for 60 sec followed by registration of the background line in the mode of the first current derivative concerning the potential with a stepwise potential change from \(-0.6 V\) to \(1.0 V\) at a scanning speed of 30 mV/s. The background solution was considered pure if no peaks on the voltammogram were detected. The height of anodic peaks was proportional to the mass concentrations of target elements in the solution. The registration of voltammograms of a “blank”, “working” sample and a “working” sample with additional elements was performed under the same operating mode. Then we added 0.01 ÷ 0.05 ml of working solutions to each glass and performed the abovementioned operation. Determined concentrations of ingredients.

Cardiac patients of both sexes aged 37–68 with a history of myocardial infarction were hospitalized to the Department of Cardiovascular Surgery of the Cardiology Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences (Head of Department – Honored Scientist of the Russian Federation V. M. Shipulin). Extensive transmural myocardial infarctions triggered ICMP development in all patients. The selection criteria for patients with post-infarct LV dilation (Fig. 1) leading to aneurysm were the LV ejection fraction less than 40%, II-IV NYHA (New York Heart Association) circulatory inefficiency, the duration of ischemic heart disease for 1–10 years, stenosis of coronary arteries of 75% or more. The exclusion criterion was organic damage of the heart valves.

Figure 1. The scheme of adverse myocardial remodeling. Source: Compiled by the authors.

To restore the standard regular LV geometry, achieve myocardial revascularization, and eliminate functional mitral insufficiency, all patients underwent surgical reconstruction of LV according to V. Dor procedure under cardiopulmonary conditions cardiopulmonary bypass condition cardiopulmonary bypass...
conditions cardioplegia (figure 2). The injured myocardium was removed through the incision in the LV aneurysm center. A purse-string suture and GoreTex patch were applied between the myocardium and scar to give the LV cavity an oval shape (figure 2).

Twelve months later, patients developed repeated LV remodeling and progression of clinical and hemodynamic signs of HF. Two main groups of patients were identified: those who have shown positive dynamics (regressive remodeling of LV) and negative dynamics (progressive postoperative remodeling of LV).

Statistical analyses were conducted using the STATISTICA 13.3 software package for Windows. The mean (X) and standard error (m) or median (Me) and 25% (Q1) and 75% (Q3) quartiles were calculated. The Kolmogorov-Smirnov test performed the normality testing. Because of the non-normal distribution, we used the non-parametric Mann Whitney U-test to detect significant differences between samples. Correlation between the parameters was established via regression analysis. A coefficient (r) values indicated statistically significant correlations with a significance level greater than 95%.

![Figure 2. LV geometry before (a) and after surgical treatment (b). Source: Compiled by the authors.](image)

### Table 1. Se concentration (mg/kg) in the hair of residents of Tomsk, X ± m.

| Group                        | Hair  |
|------------------------------|-------|
| Recommended levels for men and women * | 0.8 – 5.0 |
| Healthy residents, n=74      | 0.5 – 1.5 |
|                              | 0.90 ± 0.05 |

*Source: [4]; here and in Tables 2–3, n – number of subjects; n – number of samples.

However, the detected concentration is three times higher than the trace element level in male Hair (0.31–0.33 mg/kg) in the Se-deficient areas of the P. R. China [11]. Therefore, KD’s contribution to the pathogenesis of postoperative pathological LV remodeling in Tomsk patients is highly unlikely.

A deviation from the normal distribution was observed for Se content in LV myocardium. Data were represented as Me (Q1–Q3) (tables 2–3).

Se concentrations in the myocardium of healthy people and cardiac surgery patients 12 months after surgical LV did not have a statistically significant difference (Table 2). This could be due to the heterogeneity of surgical patients in terms of surgical outcomes.
Table 2. Concentrations of Se (mg/kg) in LV myocardium of cardiac surgery patients with ICMP, Me (Q1–Q3).

| Group                                           | LV myocardium      |
|------------------------------------------------|--------------------|
| Intact myocardium zone upon necropsy (control), n1=18 | 0.043 (0.011–0.125) |
| Zone of postoperative myocardial remodeling, n1=33          | 0.037 (0.012–0.22)  |

Source: Compiled by the authors.

We used the processes classification to divide postoperative LV myocardium changes: asymptomatic (regressive), adaptive, and maladaptive remodeling. According to echocardiography, the type was based primarily on the relative LV wall thickness (table 3).

A positive outcome of surgical intervention (improvement of the LV hemodynamic, clinical parameters) was observed in 29% of cases. 13% of patients with initial signs of adaptive LV remodeling showed reverse remodeling; 16% of the examined patients with MALR were later moved to the AR group.

The reported value of asymptomatic reverse LV remodeling (13%; Table 2) corresponds to that in [10]. Most patients (56% with AR and 84% with MALR) clinically did not respond to surgical intervention. The indices remained within the initial values. A status of 31% of patients with AR aggravated significantly after reconstructive surgery (table 3).

Interestingly, the absolute values of Se concentrations did not significantly differ (table 3). We applied elements of a personalized approach for assessing patients’ postoperative status and corresponding changes in Se level. Analysis of the shared distribution of signs has shown an absolute dependence of the outcome variant (positive-constant-negative) of postoperative modifications and the variations in Se concentrations (increase-constant-decrease) the myocardium. This tendency was detected in 4 out of 5 groups.

Table 3. Concentrations of Se in the myocardium of patients with ICMP with benign and adverse outcomes of LV postoperative remodeling, Me (Q1–Q3).

| Initial groups of cardiac surgery patients | [Se], mg/kg | One year after surgical treatment | Incidence of a benign outcome versus [Se] variations | Incidence of failure versus [Se] variations |
|-------------------------------------------|-------------|----------------------------------|-----------------------------------------------|-------------------------------------------|
| Adaptive myocardial remodeling (AR), n=96 | 0.017 (0.004-0.037) | 13% / 14% increase in [Se] | 56% / 57% of [Se] corresponds to control (table 2) | 31% / 28% decrease in [Se] |
| Maladaptive myocardial remodeling (MALR), n=57 | 0.166 (0.076-0.93) | 0 | 16% / 25% of [Se] corresponds to control (table 2) | 84% / 75% increase in [Se] |

Note: variations (correspondence, increase, or decrease) of [Se] compared with the control level in table 2.
Source: Compiled by the authors.

An exception to the assumed trend was detected in the MALR group. In 84% of the examined patients with a high (above control) background of Se content in the myocardium, a status improvement was not observed (Table 3). Regression analysis was used to determine the preliminary nature of the relationship between the outcome of LV reconstructive surgery and Se concentration in the myocardium in 4 selected groups (figure 3).
Regression analysis (figure 3) showed a linear dependence between a benign outcome of surgical intervention with a high (above control) concentration of Se, relationship between the whole state of patients with a reference value of Se, and a negative outcome versus the reduced level of trace element in LV myocardium.

![Figure 3. Linear regression between the studied indices. Source: Compiled by the authors.](image)

4. Discussion

According to a review of Mehdi et al. [6], thirty selenoproteins have been identified in recent years throughout 25 mammalian genes. There is an inverse association between selenium concentrations and ischemic heart disease incidences, especially in populations with low selenium intake or selenium status. However, some observations showed that low Se concentrations associated with cardiovascular risk should be treated as suggested [6].

In our pilot study, the typical average (near the lower border) regional level of Se in human Hair was found in Tomsk city (table 1). Concentrations of Se in the myocardium patients with ICMP do not differ from that in healthy people who died from acute trauma (Table 2). Nevertheless, a significant part of cardiac surgery patients (84% with MALR and 31% with AR) showed a negative dynamics of the postoperative myocardial remodeling with HF progression (table 3). Post-infarct LV dysfunction and cardiac remodeling are the primary causes of chronic HF, and Se has a cardioprotective effect [9]. However, regression analysis showed a close direct correlation of Se concentration only with postoperative AR outcomes and favorable MALR outcome (table 3, figure 3).

Against papers that report the positive effect of Se on cardiovascular diseases [1] the fact of negative postoperative progression of MALR (84%) in a condition of elevated (up to 2 mg/kg in some patients) Se concentrations in the myocardium turned out to be excellent (Table 3). One explanation could be the need for an optimal Se concentration for a positive effect on the body's redox processes. Indeed, recent reviews described in [6] showed a U-shape response curve between the selenium status and the risk of cardiovascular disease.

On the other hand, three main pathways are associated with most systemic complications of HF: ischemia, reperfusion injury, and perioperative inflammation [1]. Pathological postoperative LV remodeling in MALR has a more complex nature (the so-called vicious circle”) with just a little selenoproteins' involvement.
5. Conclusion
Selenium is an essential trace element in living organisms, but some aspects of its metabolism and function remain unknown. Se considerable deficiencies have been known to cause significant cardiovascular system disturbances along with LV fibrosis [3]. At the same time, an understanding of pathways that influence the role of Se in HF progression is insufficient. Therefore, clinical studies are needed to characterize SSE’s significance in post-infarct LV dysfunction and postoperative remodeling.

In this regard, Se concentrations detected in the Hair of healthy people and myocardium of ICMP patients were close to normal. However, many cardiac patients have a negative dynamics of postoperative LV remodeling with HF progression. We obtained preliminary results of a direct correlation between favorable outcomes of adaptive and maladaptive myocardial remodeling with variations of Se concentrations in the myocardium. However, some abnormal postoperative LV remodeling (MALR) cases have been detected in the presence of a high Se concentration in the myocardium. Further in-depth research is required to translate novel knowledge from the laboratory bench to the clinics.

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