International Journal of Medicine and Pharmacy
June 2015, Vol. 3, No. 1, pp. 17-26
ISSN 2372-5087 (Print) 2372-5095 (Online)

Published by American Research Institute for Policy Development
DOI: 10.15640/ijmp.v3n1a3
URL: http://dx.doi.org/10.15640/ijmp.v3n1a3

Selenium Status in Paroxysmal Atrial Fibrillation

Mariya Negreva[1], Svetoslav Georgiev[2], Katerina Vitlianova[3] & Rossitsa Georgieva[4]

Abstract

Background: Selenium deficiency is established in a number of socially important diseases. Data about selenium status in paroxysmal a trial fibrillation (PAF) are lacking. **Aim:** To study the selenium status in patients with PAF by measuring serum selenium levels during the arrhythmia and after the conversion to sinus rhythm. **Methods:** Selenium levels were measured in 33 patients (17 male, 16 female; mean age 60.03±1.93) and 33 controls (17 male, 16 female; mean age 59.27±1.72).In patients selenium was examinedupon hospitalization (baseline), on 24thhour and on 28th day after sinus rhythm restoration.In controls it was determined once. Selenium was quantified by atomic absorption spectrometry. **Results:** Mean AF duration up to hospitalization was 8.64±1.03 hours. Baseline selenium values in patients were lower than in controls (0.898±0.025 vs 0.972±0.025 μmol/L, p=0.04). On 24th hour and 28th day no significant difference was established (0.938±0.026 vs 0.972±0.025 μmol/L, p=0.35; 0.952±0.023 vs 0.972±0.025 μmol/L, p=0.55, respectively). **Conclusion:** Selenium deficiency is observed in the early hours of PAF that restores quickly after cardio version. This specific dynamics suggests a close relationship between selenium levels and PAF. Further studies are necessary to position selenium deficiency in the complex system of path physiological mechanisms of PAF manifestation and recurrences.

Keywords: Selenium, Atrial fibrillation, Pathophysiology, Sinus rhythm

[1] PhD, First Clinic of Cardiology, Varna University Hospital "St. Marina", 1 H. Smirnenski blvd, 9010 Varna, Bulgaria. Tel: +359 888 487 303; Fax: +359 52 302 881, E-mail: mnegreva@abv.bg
[2] Second Clinic of Cardiology, Varna University Hospital "St. Marina", 1 H. Smirnenski blvd, 9010 Varna, Bulgaria.
[3] Clinic of Cardiology, Second City Hospital, 120 Hr. Botev str, 1202 Sofia, Bulgaria.
[4] National Center of Public Health and Analyses, 15 Acad. I. Geshov blvd, 1431 Sofia, Bulgaria.

1. Background

Selenium (Se) was discovered over 200 years ago by the Swedish chemist Jöns Jacob Brezelius, but was determined as an essential trace element in the human organism only at the end of the 20th century when the important biological functions it is responsible for were established. Nowadays Seis primarily known for its role in antioxidant defense system as well as for its anti-inflammatory and anti-virus properties (Papp et al., 2007). Therefore, it is subject to investigations in a number of socially significant diseases. Its deficiency is associated with increased risk of malignant, infectious and some neurological diseases such as Alzheimer's disease and Parkinson's disease (Rayman, 2000).Changes in the Se status are also established in cardiovascular diseases. Acute myocardial infarction with future cardiovascular death is associated with reduced concentrations of the trace element(Lubos et al., 2010).The epidemiological studies have established a reverse correlation between Selevels in blood and the risk for cardiovascular events, the results, however, being unconvincing from a statistical point of view(Tanguy et al., 2012; Joseph, 2013). In a recent investigation, the additional intake of Se has not demonstrated a protective effect in terms of cardiovascular morbidity and mortality (Rayman, 2012). Atrial fibrillation (AF) is the commonest rhythm disorder in clinical practice and is defined as the new "non-contagious epidemics" (Serranoa et al., 2009). Paroxysmal atrial fibrillation (PAF), which occurs in25% to 62% of all AF cases, is characterized by frequent recurrences and a high thromboembolic potential (Serranoa et al., 2009; Chugh et al., 2001). Due to the relatively low efficiency of the anti-arrhythmic treatment administered so far, the intricate mechanisms related to the clinical manifestations of PAF present special interest for scientific research. In this respect, studies of the Se status in PAF are lacking.

2. Aim

To study the Se status in patients with PAF by measuring serum Se levels during the arrhythmia episode and after the conversion to sinus rhythm.

3. Patients and Methods

3.1. Study Population

For the purpose of the study, a total of 338 patients with PAF were screened. An obligatory inclusion criterion for screening was a history of the arrhythmia episode less than 48 hours, which could allow for an acute pharmacological conversion to sinus rhythm. The span of the arrhythmiaup to the moment of hospitalization was accurately determined based on detailed history taking. The diagnosis of AF was accepted only on the base of ECG performed immediately after the patients' admission to hospital. An attempt for cardio version of PAF was made by administration of the ant arrhythmic drug*propafenone* according to the well-established regimen and rules, under constant rhythm monitoring (Bellandi et al, 1995; Bianconi et al., 1998). Due to the presence of exclusion criteria (enumerated below), only 37 patients (21 male, 16 female) remained in the study. All of them were with successfully restored sinus rhythm. No relapses of the rhythm disorder were established during the two follow-up check-ups performed on the seventh and twenty-eighth day after the PAF discontinuation. To equalize the gender structure of the group, 33 patients were consecutively selected for the study (17 male and 16 female) of mean age 60.03±1.93 years. In order to eliminate the impact of the nutritional daily intake on Se levels, all patients remained on their usual diet during the whole period of the study. The same exclusion criteria were applied to the formation of the control group (see below). Thus, out of a total of 169 screened, 33were selected as controls for the study (17 male, 16 female, mean age 59.27±1.72). Controls had no history or ECG data for AF. The study was conducted in the First Clinic of Cardiology at University Hospital "St. Marina"- Varna in the period October 2010 – May 2012, after the approval of the Ethical Commission on Scientific Research at the above hospital and in accordance with the requirements of the Helsinki Declaration (WMA Declaration of Helsinki, 2008). The participants were included in the study after prior informed consent for participation.

Exclusion criteria for the study:

1. Cardiovascular diseases: ischemic heart disease; heart failure; uncontrollable hypertension; implanted device for the treatment of rhythm disorders; inflammatory or congenital heart diseases; moderate or severe acquired valvular defects.

2. Other diseases: renal or liver failure; inflammatory, infectious, neoplasmic, autoimmune or central nervous system diseases; diseases of the endocrine nervous system (except for diabetes mellitus type 2, non-insulin dependent, well controlled).
3. Drugs: hormone-replacement therapy or contraceptives; systematic intake of analgesics, incl. non-steroidal anti-inflammatory drugs.
4. Inability to precisely specify the arrhythmia onset*(only for patients)*.
5. Persistence of the arrhythmia after *propafenone*administration; recurrence of AF during the study period (28 days after sinus rhythm restoration);convertion of PAF by electrical cardioversion*(only for patients)*.

3.2. Study Protocol. Sample Collection and Analysis

Selenium status in patients with PAF was investigated by means of triple examination of Se levels, namely immediately after hospital admission (baseline values), 24 hours and 28 days after sinus rhythm restoration. In controls the trace element was determined only once. Selenium levels were investigated in serum obtained from venous blood collected into a vacutainer VACUETTE/4.0 ml/Serum Sep. The blood was centrifuged at 600 g for 10 min and serum was frozen and kept at -70 ºC for up to six months. The trace element content was determined by means of electro-thermal atomic absorption spectrometry (AAS) at wavelength 196.0 nm and band pass 2 nm, upon 4-fold dilution of the samples with 1% v/v Triton X-100 in 0.2% v/v HNO3. A Model 4110 ZL Perkin-Elmer AAS with a transverse heated graphite atomizer (THGA) and longitudinal Zeeman-effect background correction was used for direct AAS measurements; 10 μl of the samples and 10 μl of rhodium modifier (10 μg Rh) were injected into the THGA; pyrolysis and atomization temperatures were 1100 C° and 2100 C°, respectively; an extra cleaning step at 2400 Cº (1+5s) was required; matrix-matched calibrations was applied (Tsalev et al., 2001; Karmaus et al., 2008). The final results were calculated as a mean value of two parallels, each with two replicates. The internal quality control was performed by analysis of certified reference material Seronorm TM Trace Elements Serum, Level 2, SERO AS, Norway. The data obtained (1.67 ±0.06 μmol/l, n=7) were in good agreement with the certified value 1.63 μmol/l (1.53 – 1.73 μmol/l).

3.3. Statistical Analysis

The mean values, the standard error of the mean (SEM) and relative shares were calculated by descriptive statistics. The analysis of the hypotheses for differences of two means and the relative share equality was done by means of the Student's t-test. The statistical significance was accepted if $p<0.05$.

The results were presented as a mean value±SEM or n(%). Data analysis was carried out means of software product Graph Pad Prism 5.

4. Results

The group of the patients was statistically identical with that of the controls in terms of the following indicators: number of participants in a group, mean age, gender structure, accompanying diseases, dyslipidemia, harmful habits and BMI ($p>0.05$) (Table 1).

Table 1: Demographic and Clinical Characteristics of Patients' and Control Group

	Patients with PAF Number (%)	Control group Number (%)	P value
Number of participants in a group	33	33	1
Mean age (years)	60.03±1.93	59.27±1.72	0.77
Men/Women	17/16	17/16	1
Accompanying diseases			
Hypertension	21 (63.64%)	24 (73.73%)	0.38
Diabetes mellitus type 2	1 (3.03%)	1 (3.03%)	1
Dyslipidemia	3 (9.09%)	1 (3.03%)	0.30
Harmful habits			
Smoking	4 (12.12%)	7 (21.21%)	0.32
Alcohol intake	4 (12.12%)	6 (18.18%)	0.49
BMI (kg/m²)	23.86±2.84	23.98±2.75	0.86

The statistical analysis showed that the mean AF episode duration before patients' hospitalization was 8.64±1.03 hours. All the patients were admitted to the ward between the second and the twenty fourth hour after the onset of the rhythm disorder. Upon the patients' admission to the ward, the Se levels were lower than those in the controls (0.898±0.025 vs 0.972±0.025 μmol/L, p=0.04). Twenty-four hours following the restoration of the sinus rhythm, the levels of the trace element measured in the patients did not differ statistically from those in the controls (0.938±0.026 vs 0.972±0.025 μmol/L, p=0.35). On the 28th day after the rhythm regularization, no significant differences were observed again (0.952±0.023 vs 0.972±0.025 μmol/L, p=0.55).

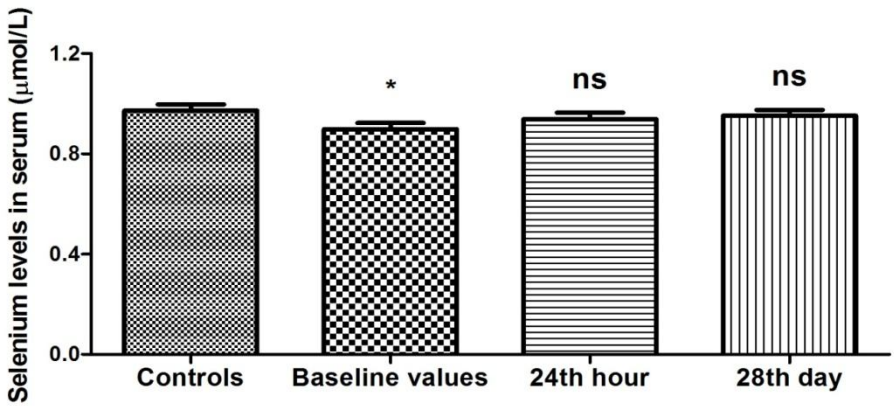

Figure 1: Serum selenium levels in patients with PAF (μmol/L)

(baseline values – values measured upon hospitalization; 24th hour – values measured 24 hours after cardioversion; 28th day – values measured 28 days after cardioversion; * - $p<0.05$; ns – statistically not significant)

5. Discussion

Selenium status in human organism could be assessed by measurement of Se content in hair, toenails and urine, or more directly by measurement of Se levels in blood (serum, plasma or erythrocytes). Selenium in hair and toenailsis a good long-term biomarker of Se status. Serum Se is a useful indicator of the short-term changes and isamong the commonest biomarkers for the evaluation of the Se status in the human organism (Fairweather-Tait et al., 2011). These facts give us ground to assume that Se status in our patients with PAF isreliably presented by means of serum Se levels. It is relevant here to be mentioned that serum Se levels are affected by some factors as age, gender, smoking and alcoholism (Olivieri et al., 1994; Arnaud et al., 2012; Kocyigit et al., 2001; Luty-Frackiewicz et al., 2002). Therefore, the unification of our patients' and control groups in terms of these indicators (Table 1) enables the maximum elimination of their influence on Se levels, thus making the comparison between the two groups objective to a maximum degree. As presented on Figure 1, baseline Se values in patients with PAF were significantly lower that presents deficiency of the trace element still in the first twenty-four hours of the clinical manifestation of the rhythm disorder. It is well-known that the physiological functions of Se are closely related with its content in the human organism. Furthermore, they depend almost entirely on Se incorporation in selenoproteins under the form of the 21st amino acid, selenocystein (Sec)(Lu et al., 2009).

Evidence for the significance of Sec, and Se respectively, can be found in the studies conducted by Gasdaska et al. andLee et al., in which the substitution of Sec with cysteine in selenoproteinsleads to a dramatic loss of enzyme activity (Gasdaska et al., 1999; Lee et a., 2000). So far, over 35 selenoproteins have been discovered that are involved inredox signaling, antioxidant and immune systems as well as in thyroid hormone metabolism (Pepe et al., 2008). Changes in Se blood levels lead to changes in the enzyme activity of the selenoproteins (Lu et al., 2009). Se deficiency is associated with major decrease in selenoproteins' activity, including that of glutathione peroxidase (GSH-Px) andthioredoxin reductase (TrxRs). These enzymes are among the indispensable components of the antioxidant defense system. The function of GSH-Px is linked to the neutralization of organic peroxides (ROOH) and hydrogen peroxide (H_2O_2):

$$\mathbf{ROOH} + 2GSH \xrightarrow{\text{GSH-Px}} ROH + GSSG + H_2O$$

$$\mathbf{H_2O_2} + 2GSH \xrightarrow{\text{GSH-Px}} 2H_2O + GSSG$$

These processes limit the peroxidation of lipid biomolecules and protect the cells from oxidative damage (Brigelius-Flohé, et al., 2013). A strong correlation exists between Se deficiency and oxidative stress (Ducros et al., 2004; Meschy, 2010). Trx Rsarevital for the maintenance of the oxidative balance as well. They maintain the Trx/TrxR system in a reduced state for elimination of hydrogen peroxide (Chugh et al., 2001). Reduced activity of GSH-Px and TrxRs is a prerequisite for the domination of the pro-oxidative processes over antioxidant protection and therefore for the development of oxidative damages. A major substrate for AF clinical manifestation and recurrences is the so-called "electrical remodeling" of the atria. It is observed even after a short AF episode and histological studies establish its association with oxidative changes in cardiomyocytes, respectively with oxidative stress (Carnes et al., 2001; Yehet al., 2011). The important role of Se in the antioxidant system of the human organism gives us serious grounds to assume that the deficiency of the trace element could cause the above mentioned histological, respectively electrophysiological changes in the atria. That is why the changes we established in Se status could probably be linked to the complex mechanisms of AF manifestation, retention and recurrences. We were particularly interested in the results on the 24th hour and the 28th day after cardio version. The restoration of the sinus rhythm is associated with an increase in the levels of Se to absence of a statistically significant difference between the patients and the controls (Figure 1).

The specific dynamics once again suggests a close relation between Se deficiency and the presence of PAF. It also risesthe question about the mechanisms of Se homeostasis. The major source of serum Se is Selenoprotein P thatis synthesized in the liver. It contains approximately 50% of the total amount of serum Se and its production in hepatocytes is central to Se homeostasis (Hill et al., 2012). Bearing in mind the enhanced synthesis of proteins in the liver as well as the rapid dynamics in Se levels, we can assume a dominating role of the liver, in particular.

Conclusion

In patients with PAF, the status of the trace element selenium is altered. Still in the early hours of the rhythm disorder, reduced serum Se levels are observed, which on the 24th hour after the restoration of the sinus rhythm increase and become statistically equal with those of the controls. The specific dynamics of the Selevels suggests a close relationship between the Se status and the clinical course of PAF. Further studies are necessary to position the Se deficiency in the complex system of path physiological mechanisms responsible for the manifestation and recurrences of PAF.

References

Arnaud, J., de Lorgeril, M., Akbaraly, T., Salen, P., Arnout, J., Cappuccio, F. P., van Dongen, M. C., Donati, M. B., Krogh, V., Siani, A., Iacoviello, L.(2012). Gender differences in copper, zinc and selenium status in diabetic-free metabolic syndrome European population - the IMMIDIET study. Nutr Metab Cardiovasc Dis. 22(6), 517-524. doi: 10.1016/j.numecd.2010.09.005.

Bellandi, F., Cantini, F., Pedone, T., Palchetti, R., Bamoshmoosh, M., Dabizzi, R. (1995). Effectiveness of Intravenous Propafenone for Conversion of Recent-Onset Atrial Fibrillation: A Placebo-Controlled Study. Clin Cardiol. 18, 631-634.

Bianconi, L., Mennuni, M. (1998). Comparison Between Propafenone and Digoxin Administered Intravenously to Patients With Acute Atrial Fibrillation. Am J Cardiol. 82, 584-588.

Brigelius-Flohé, R., Maiorino, M. (2013). Glutathione peroxidases. Biochim Biophys Acta. 1830(5), 3289-3303. doi: 10.1016/j.bbagen.2012.11.020.

Carnes, C. A., Chung, M. K., Nakayama, T., Nakayama, H., Baliga, R. S., Piao, S., Kanderian, A., Pavia, S., Hamlin, R. L., McCarthy, P. M., Bauer, J. A, Van Wagoner, D. R. (2001). Ascorbate Attenuates Atrial Pacing-Induced Peroxynitrite Formation and Electrical Remodeling and Decreases the Incidence of Postoperative Atrial Fibrillation. Circulation Research. 89, e32-e38,

Chugh, S. S., Blackshear, J. L., Shen, W., Hammill, S. C., Gersh, B. J. (2001). Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol. 37(2), 371-378. doi:10.1016/S0735-1097(00)01107-4.

Ducros, V., Favier, A. (2004). Selenium metabolism. EMC Endocrinol. Nutr. 1, 19–28.

Fairweather-Tait, S. J., Bao, Y., Broadley, M. R., Collings, R., Ford, D., Hesketh, J. E., Hurst, R.(2011). Selenium in human health and disease.Antioxid Redox Signal. 14(7), 1337-1383. doi: 10.1089/ars.2010.3275.

Gasdaska, J. R., Harney, J. W., Gasdaska, P. Y., Powis, G., Berry, M. J. (1999). Regulation of human thioredoxin reductase expression and activity by 3'-untranslated region selenocysteine insertion sequence and mRNA instability elements. J Biol Chem. 274, 25379–25385.

Hill, K. E., Wu, S., Motley, A. K., Stevenson, T. D., Winfrey, V. P., Capecchi, M. R., Atkins, J. F., Burk, R. F. (2012). Production of selenoprotein P (Sepp1) by hepatocytes is central to selenium homeostasis. J Biol Chem. 287(48), 40414-40424. doi: 10.1074/jbc.M112.421404.

Joseph, J. (2013). Selenium and cardiometabolic health: Inconclusive yet intriguing evidence. Am. J.Med. Sci. 346(3), 216-220. doi: 10.1097/MAJ.0b013e3182638716.

Karmaus, W., Dimitrov, P., Simeonov, V., Tsolova, S.,Bonev, A., Georgieva, R. (2008). Metals and kidney markers in adult offspring of endemic nephropathy patients and controls: a two-year follow-up study. Environ Health. **7**-11. doi:10.1186/1476-069X-7-11.

Kocyigit, A., Erel, O., Gur, S. (2001). Effects of tobacco smoking on plasma selenium, zinc, copper and iron concentrations and related antioxidative enzyme activities. Clin Biochem. 34(8), 629-633.

Lee, S. R., Bar-Noy, S., Kwon, J., Levine, R. L, Stadtman, T. C., Rhee, S. G. (2000). Mammalian thioredoxin reductase: oxidation of the C-terminal cysteine/ selenocysteine active site forms a thioselenide, and replacement of selenium with sulfur markedly reduces catalytic activity. Proc Natl Acad Sci USA. 97, 2521–2526.

Lu, J., Holmgren, A. (2009). Selenoproteins. JBC. 284(2), 723-727.

Lubos, E., Sinning, C. R., Schnabel, R. B., Wild, P. S., Zeller, T., Rupprecht, H. J., Bickel, C., Lackner, K. J., Peetz, D., Loscalzo, J., Munzel, T., Blankenberg S. (2010). Serum selenium and prognosis in cardiovascular disease: results from the AtheroGene study. Atherosclerosis. 209, 271–277.

Luty-Frackiewicz, A., Jethon, Z., Januszewska, L. (2002). Effect of smoking and alcohol consumption on the serum selenium level of Lower Silesian population. Sci Total Environ. 285(1-3), 89-95.

Meschy, F. (2010). Nutrition minérale des ruminants; Editions Quae: Versaille, France, p. 208.

Olivieri, O., Stanzial, A. M., Girelli, D., Trevisan, M. T., Guarini, P.,Terzi, M., Caffi, S., Fontana, F., Casaril, M., Ferrari, S. (1994). Seleniumstatus, fatty acids, vitamins A and E, and aging: theNove Study. Am J Clin Nutr. 60, 510–517.

Papp, L. V., Lu, J., Holmgren, A., Khanna, K. K. From selenium to selenoproteins: synthesis, identity, and their role in human health. (2007). Antioxid Redox Signal. 9(7), 775-806.

Pepe, S., Leong, J.Y., Van der Merwe, J., Marasco, S. F., Hadj, A., Lymbury, R., Perkins, A., Rosenfeldt, F.L. (2008). Targeting oxidative stress in surgery: effects of ageing and therapy. Exp Gerontol. 43(7), 653-657. doi: 10.1016/j.exger.2008.03.011.

Rayman, M. P. (2000). The importance of selenium to human health. Lancet. 356, 233–241.

Rayman, M. P. (2012). Selenium and human health. Lancet. 379, 1256–1268.

Serranoa, M. C., Hernández-Madrida, A.(2009). Atrial Fibrillation. Is it an Epidemic?Rev Esp Cardiol. 62,10-14. DOI: 10.1016/S1885-5857(09)71508-7.

Tanguy, S., Grauzam, S., de Leiris, J., Boucher, F. (2012). Impact of dietary selenium intake on cardiachealth: Experimental approaches and human studies. Mol. Nutr. Food Res. 56, 1106–1121.

Tsalev, D. L., Lampugnani, L., D'Ulivo, A., Petrov, I. I. Jr., Georgieva,R., Marcucci, K., Zamboni, R.(2001). Electrothermal atomic absorption spectrometric determination of selenium in biological fluids with rhodium modifier compared with hydride generation atomic spectrometric techniques.Microchem J.70(2), 103-113.

World Medical Association Declaration of Helsinki. (2008). Ethical principles for medical research involving human subjects. 59th WMA General Assembly. Seoul.

Yeh, Y. H., Kuo, C. T., Chan, T. H., Chang, G. J., Qi, X. Y., Tsai, F., Nattel, S., Chen, W. J. (2011). Transforming growth factor-β and oxidative stress mediate tachycardia-induced cellular remodelling in cultured atrial-derived myocytes. Cardiovasc Res. 91(1), 62-70.