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SUMMARY

**CARDIAC ARRHYTHMIAS IN YOUNG PEOPLE - THE VALUE OF
OXIDATIVE STRESS BIOMARKERS, GENETIC POLYMORPHISMS
AND EARLY ENDOTHELIAL DYSFUNCTION RISK**

SCIENTIFIC COORDINATOR:

Prof. Univ. Dr. DOINA CÂRSTEA

PHD STUDENT:

MARIA CRISTINA BEZNĂ

CRAIOVA

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Key words: cardiac arrhythmias, youngs, oxidative stress, superoxide dismutase, glutathione peroxidase, total antioxidant capacity, oxidized-LDL, anti-oxidized-LDL antibodies, dyslipidemia, genetic polymorphisms

INTRODUCTION

Cardiac arrhythmias, in young people, represent a highly interesting field, through its immediate and long-term pathological implications. Frequently described, they have a significant medical and social impact on the quality of life and on professional or extra-professional performances.

The multitude of factors favoring the installation of rhythm disorders, functional or non-functional, paroxysmic, repetitive, persistent or permanent, required a study of their profile, as well as of modifications in oxidative stress, metabolic, immune status and in genetic polymorphisms that may be involved in arrhythmic pathology initiation or in subsequent long-term lesional pathologies.

PhD thesis: "Cardiac arrhythmias in young people - the value of oxidative stress biomarkers, gene polymorphisms and early endothelial dysfunction risk" represents a topic of current scientific interest, studying a frequent pathology, regarding cardiac arrhythmias in young people, present from non-significant haemodynamic clinical forms, to those with hemodynamic significance and serious complications.

The originality of this research consists in demonstrating the oxidative stress (through biomarkers - superoxide dismutase, glutathione peroxidase and total antioxidant capacity) and genetic polymorphisms involvement (superoxide dismutase2-rs4880 and inducible nitric oxide synthase-rs2297518) in the development of arrhythmic potential in young people as well as in identifying possible lipid abnormal oxidations (through oxidized-LDL), together with the development of an immune pathogenesis (anti-oxidized-LDL antibodies) and the risk of early endothelial dysfunction in young people with or without a dyslipidemic background.

I. GENERAL PART: STATE OF KNOWLEDGE

1. CARDIAC ARRHYTHMIAS

Cardiac arrhythmias represent a heterogeneous group of electrical heart disorders, which may or may not be associated with underlying structural cardiac pathology [1]. Cardiac rhythm disorders are manifested when a substrate with arrhythmogenic predisposition is present, upon which various triggering, disturbing and perpetuating factors act. Dysrhythmias, both worldwide and european, affect 0,6-1,5% of the general population, being 3 times more common in females than in males and 2 times more frequent in elderly than in young people [1]. Prevalence among the general population is 1,25/1000, with an incidence of 28/100000 [1,2,3].

2. DYSLIPIDEMIA. MIOCARDIAL METABOLIC ASSESSMENT WITH ARRHYTHMIC CARDIAC IMPLICATIONS

Dyslipidemia, important in triggering a cardiovascular pathology, is a potentially influential risk factor, both by modifying lifestyle and by pharmacologically active medication [1,4,5]. Hypercholesterolemia is proatherogenic and associated with induction of: cardiac contractile properties dysfunctions [7,8], ionic disorders, increased levels of oxidative stress and myocardial remodeling [1,2,6,9,10,11]. Mechanisms through which dyslipidemia induces rhythm disturbances: stimulates ischemia induced by the presence of oxidative stress; QT interval is prolonged and heterogeneous; performs cardiac remodeling; increases sympathetic tone; disturbs the balance of transmembrane ion exchanges; increases the incidence of late ventricular potential. Dyslipidemia has implications also in endothelial dysfunction and the development of atherosclerosis, as well as in oxidation processes, generating oxidized-LDL [9-13].

3. OXIDATIVE STRESS AND CARDIAC DYSRHYTHMIAS

Oxidative stress, involved in various conditions [11-16], in order to determine its level, requires specific biomarkers: superoxide dismutase (SOD), glutathione peroxidase (GPx), total antioxidant capacity (TAS), oxidized-LDL, anti-oxidized-LDL [14]. Their level is a predictive and prognostic factor for the reactivity of the body to the action of oxidative stress. Excess production of reactive species is an important risk factor in the development of cardiovascular diseases, especially cardiac insufficiency, arrhythmias, atherosclerosis (by lipid oxidation within vascular intimal level) [14,15].

4. GENETICS – IMPLICATIONS INCARDIAC ARRHYTHMIC PATHOLOGY

Genetic polymorphisms represent the incidence of two or more phenotypic patterns, determined by genetic mechanisms, through the presence of various alleles. The study of genetic polymorphisms is particularly useful for early diagnosis and screening.

Polymorphism of SOD2 rs4880, g.160113872A> G: SOD2 is a mitochondrial-type enzyme. Its variations are a consequence of hydrogen peroxide and reactive oxygen species actions, being able, by feedback mechanism or by the variability of transcription factors, to inhibit SOD2 activity [15,16].

Polymorphism of iNOS rs2297518, g.26096597G>A: iNOS gene is located on chromosome 17 (17q11.2-12) and is involved in a wide range of conditions [22]. This enzyme forms the nitric oxide, that plays a key role in the immune response.

II. SPECIAL PART: RESEARCH AND PERSONAL CONTRIBUTIONS

1. MOTIVATION, PURPOSE AND OBJECTIVES

The motivation and purpose of the research is to achieve a prospective study regarding cardiac rhythm disorders in young people, in relation to clinical, biochemical and genetic factors, which may constitute an arrhythmic risk pattern, as well as the assessment of early endothelial dysfunction risk, with subsequent vascular, tissues and visceral severe complications, which may represent a therapeutic target in primary prevention.

2. PATIENTS, MATERIAL AND METHODES

The study was conducted on 180 young, caucasian subjects, from Oltenia region. The methodology included: evaluation of clinical and diagnostic subjects data specific for the research: lipid profile (oxidized-LDL, anti-oxidized-LDL antibodies), oxidative stress (superoxide-dismutase-SOD, glutathione peroxidase-GPx, total antioxidant capacity-TAS); genetic determination of mononucleotide polymorphisms of SOD2 (rs207AA559) and iNOS (rs22975AA8) genes; statistical and mathematical analysis. Determinations were achieved in: General and Applied Biochemistry Laboratory of Pharmacy Faculty, Human Genomics Laboratory and Department of Computer Science, at the University of Medicine and Pharmacy from Craiova.

3. RESULTS

3. 1. CLINICAL RESULTS : The study was conducted on 180 subjects, divided into three groups, of which: two groups of 40 patients each (Lot I and Lot II), with cardiac arrhythmias, with and without dyslipidemia, and a control group, consisting of healthy subjects (Lot III).

3.2. BIOCHEMICAL RESULTS

Superoxide dismutase (SOD): Compared to the control group (healthy subjects), in group I, mean SOD values were decreased to 61,68%, with a deficit of 38,32%. In case of lot II, compared to the values of lot III, the average SOD value decreased to 61.77%, the deficit being of 38.23%.

Glutathione peroxidase (GPx): Compared to the control group (healthy subjects), in group I, GPx values were lowered to 68,10%, with a deficit of 31.90%. In case of lot II, compared to the values of group III (healthy), GPx decreased to 73.57%, the deficit being of 26.43%.

Total antioxidant capacity (TAS): Compared to the control group (healthy subjects), group I, TAS values were reduced to 52.34%, with a deficit of 47.66%. In the case of lot II, compared to the values of group III (healthy), TAS decreased to 54.11%, the deficit being 45.89%. Oxidized-LDL (LDL-ox): Compared to control values, oxidized LDL was twice increased in group I (205.77%), but also in group II, representing 161.46%, with an excess of 105.77% for the group of patients with dyslipidemia and of 61.46% for those without dyslipidemia. Anti-oxidized-LDL antibodies (AntiLDLox): The mean values of anti-oxidized-LDL antibodies were: in the control group: 100%, in the group of young people with arrhythmias and dyslipidemia (I): 175.82% and in the group with arrhythmias, without dyslipidemia (II): 140.22%.

3.3. GENETIC RESULTS

Polymorphism of SOD2 rs4880 (160113872A>G) gene

The predominance of heterozygous AG form was observed in all three groups (I – 59.46%, II – 45.95%, III – 48.42%); in patients with arrhythmias and dyslipidemia, the GG form is more frequent (37.84%) compared to AA (16.22%); those with arrhythmias without dyslipidaemia have a higher frequency of AA (21.62%) than of GG (18.92%).

Polymorphism of iNOS rs2297518 (26096597G>A) gene

By genotyping iNOS rs2297518, the presence of predominant homozygous GG form (I – 65.71%, II - 58.33%, III - 73.33%) was observed in all three groups; variations were found in arrhythmic patients with dyslipidaemia, who had a higher percentage for heterozygous AG genotype (38.89%) versus AA homozygous genotype (2.78%); in patients with arrhythmia without dyslipidemia the percentages of AG type (28.57%) was higher than AA (5.71%), and for the control group, AG (24.44%) was more representative than AA (2.22%) type.

4. DISCUSSIONS

Discussion of clinical data: Subjects had an average age of about 35 years for group I, 34 years for group II and 31 years for the control group, without associated pathological status except for cardiac arrhythmias in groups I-II and dyslipidemia in group I.

Discussion of biochemical, oxidative stress, lipid and immune perturbations data

Superoxide dismutase records a mean deficit in patients with arrhythmias compared to the controls, with statistical significance, which argues the involvement of this enzyme in the creation of oxidative stress and thereby the participation of excess oxygen free radicals in the genesis of arrhythmias.

Glutathione reductase recorded a statistically significant decrease ($p < 0.001$) in patients with arrhythmias. Regarding the arrhythmic profile, variations have been observed in the decrease of GPx values.

Total antioxidant capacity recorded decreasing values, approximately by half, for patients with arrhythmia, with and without dyslipidemia, compared to the controls.

The decrease of all three discussed parameters correlates highly statistically significant with the presence of arrhythmias, regardless of the presence or not of the metabolic disturbance, SOD, GPx and TAS being considered biomarkers of oxidative stress, which are important in triggering arrhythmogenic potential in young people. A series of studies [16,17,18] show that arrhythmias and oxidative stress levels are correlated, as well as oxidized-LDL [19,20].

Oxidized-LDL assessment showed that the mean value of LDL-ox increased compared to the controls mean. Although LDL increase is important in the occurrence of oxidized-LDL, in the case of increased oxygen free radicals due to enzymatic or total antioxidant deficiency (decreased SOD, GPx, TAS), this oxidation-modifying process of low density lipoproteins occurs even at a normal plasmatic level, causing oxidation of LDL, creating the premise of both subintimal deposition and also generation of anti-oxidized-LDL antibodies, in order to determine immuno-inflammatory responses.

Studies [18,19] shown that LDL-ox is correlated with endothelial dysfunction, cardiac remodeling and is considered an accelerating factor in increasing the incidence of cardiac pathology since young ages.

Determination of anti-oxidized-LDL antibodies in patients with elevated levels of oxidized-LDL argues the intervention of the immune process, reactive to LDL oxidation. Although apparently arrhythmias in young people have no significance related to endothelial dysfunction, rather than as pathological association, the link is represented by the existence of oxidative stress proven by biomarkers (SOD, GPx, TAS), which, on the one hand, may be involved in the arrhythmogenic potential (a true "electric battery") intervening in molecular and electrical mechanisms and, on the other hand, creating the background for the oxidation of low-density lipoproteins that become qualitatively modified and thus immunogenic (argued by increasing LDLox and antiLDLox), predictably generating early endothelial dysfunction.

Discussion of genetic data – genetic polymorphisms

The frequency of SOD2 and iNOS genes genotypes argued the existence of associations between the genes involved and the susceptibility to develop oxidative stress, with implications both in cardiovascular and immune-metabolic pathology. The data respected Hardy-Weinberg balance.

Study of SOD2 rs4880 (160113872A>G) gene polymorphism

Genotypic modifications of SOD2 may argue for differences in SOD activity and its deficiencies, oxidative stress inductors, with potential implications for arrhythmogenesis and lipid oxidation.

Study of iNOS rs2297518 (26096597G>A) gene polymorphism

A higher proportion of AG genotype than GG was observed in the group of dyslipidemic, with arrhythmias patients, compared to non-dyslipidemic, arrhythmic ones, with even greater differences compared to the control group.

In various studies [21,22] the involvement of certain genotypes in contractile dysfunction, cardiac arrhythmias, from young ages was highlighted.

5. CONCLUSIONS

GENERAL CONCLUSIONS

1. Arrhythmogenic potential and cardiac arrhythmias in young people include, in their etiopathogenic spectrum, modifications in oxidative stress (metabolic and immune), genetic polymorphisms, as well as predictive factors of early endothelial dysfunction, whose current research is important and of interest.

2. In the demonstration of oxidative stress and reactive oxygen species augmentation, enzymatic assays of SOD, GPx, as well as TAS, which show variations in patients with cardiac arrhythmias, with or without dyslipidemia, are useful as biomarkers.

3. SOD showed mean values decreases of approximately 62%, highly statistically significant, in all patients with arrhythmias, both in the dyslipidemia (61.68%) and in the non-dyslipidemia groups (61.77%), compared to healthy controls.

4. Cardiac arrhythmias profile and SOD deficiency in non-dyslipidemia patients was, in order: atrial flutter - 51% antioxidant SOD deficiency, atrial fibrillation - 42%, sinus bradycardia - 41%, atrial extrasystolic arrhythmia - 39%, sinus tachycardia - 37%, ventricular extrasystolic arrhythmia - 35%, supraventricular paroxysmal tachycardia - 34%, associated arrhythmias - 32% and in dyslipidemia ones: atrial fibrillation - 41%, associated arrhythmias - 40%, supraventricular paroxysmal tachycardia - 39%, sinus tachycardia - 38%, sinus bradycardia - 37%, ventricular extrasystolic arrhythmia - 36%, atrial flutter - 36%, atrial extrasystolic arrhythmia - 35%.

5. GPx recorded decreased mean values of approximately 68% in young people with heart rhythm disorders (68.10% in dyslipidemics) and 74% (73.57% in non-dyslipidemics), being highly statistically significant compared to controls.

6. Cardiac arrhythmias associated with GPX deficiency were, in order, in non-dyslipidemic patients: atrial flutter with an antioxidant GPx deficit of 33%, associated arrhythmias - 31%, sinus tachycardia - 30%, sinus bradycardia - 29%, ventricular extrasystolic arrhythmia - 28%, atrial fibrillation - 27%, atrial extrasystolic arrhythmia - 27%, supraventricular

paroxysmal tachycardia - 18% and in those with dyslipidemia: sinus bradycardia with an antioxidant GPx deficit of 35%, associated arrhythmias - 35%, sinus tachycardia - 33%, atrial fibrillation - 33%, atrial flutter - 32%, atrial extrasystolic arrhythmia - 32%, ventricular extrasystolic arrhythmia - 30%, supraventricular paroxysmal tachycardia – 26%.

7. TAS, globally expressing antioxidant activity, was reduced to about 52%-54%, highly statistically significant compared to healthy, in all young subjects with cardiac dysrhythmias (for dyslipidemic patients 52.34% and for non-dyslipidemic 54.11%).

8. TAS-deficient cardiac arrhythmias were, in order, in patients without dyslipidemia: associated arrhythmias, with a 60% antioxidant TAS deficit, sinus bradycardia - 59%, atrial fibrillation - 55%, sinus tachycardia - 48%, atrial extrasystolic arrhythmia - 43%, ventricular extrasystolic arrhythmia - 40%, supraventricular paroxysmal tachycardia - 34%, atrial flutter - 33%, and for those with dyslipidemia: atrial flutter - 62%, sinus tachycardia - 51%, associated arrhythmias - 50%, sinus bradycardia - 50%, atrial fibrillation - 49%, atrial extrasystolic arrhythmia - 44%, ventricular extrasystolic arrhythmia - 43%, supraventricular paroxysmal tachycardia - 37%.

9. The enzymatic antioxidant deficiencies of SOD (38%), GPx (32% - 26%) and TAS (48% - 46%) in all young people with cardiac arrhythmias argue for the existence of oxidative stress and its involvement in arrhythmogenesis. Moreover, by statistically significant association with the elevated LDL oxidation level and that of anti-oxidized-LDL antibodies, they interfere in the early generation of endothelial dysfunction.

10. Assessed arrhythmogenic and oxidative stress risk factors were statistically significant, especially smoking (SOD decreased to 59%) and poor vegetables nutrition (TAS decrease to 43%) in dyslipidemics. Coffee, by its antioxidant effect was considered mostly pro-arrhythmogenic, associating only small oxidative modifications (TAS decreased to 56% for dyslipidemic consumers and to 44% for non-consumers).

11. The existent oxidative stress, due to oxygen reactive species excess, favors marked oxidations, especially of lipoproteins, revealed by increased oxidized-LDL levels (regardless of initial LDL value), especially in those with oxidative stress and dyslipidemia, but in a lower percentage for those with normal LDL level.

12. The level of oxidized-LDL was increased twice (205.77%) in patients with arrhythmias and dyslipidemia, and of about one and a half (161.46%) in those without dyslipidemia.

13. The anti-oxidized-LDL autoantibodies were identified, in increased amounts, in those with excess of oxidized-LDL, regardless of their lipid status (increases to 175.82% for those with dyslipidemia and to 140.22% for those without).

14. There are statistical correlations between arrhythmias and levels of SOD, GPx, TAS, LDLox and antiLDLox antibodies. The most important are: the inverse proportionality between the decrease of SOD and the increase of LDLox and the direct one, between the increase of LDLox and the antiLDLox in the dyslipidemic subjects, as well as the inverse proportionality between the decrease of GPx and the increase of LDLox in the non-dyslipidemic ones.

15. Genetic determinations, through the study of mononucleotide polymorphisms, were useful in describing a particular substrate regarding SOD2 and iNOS genes.

16. The predominance of AG genotypes for SOD2 gene and of GG for iNOS in arrhythmic disturbances with increased cardiovascular risk was observed.

17. The profile of early endothelial dysfunction risk in young people with arrhythmias includes: decrease of antioxidants, increase of oxidative stress, favoring LDL oxidation, modification of its quality (turning it into oxidized LDL) and the development of anti-oxidized-LDL antibodies.

18. Arrhythmogenesis, oxidative stress, early lipoprotein oxidations, as well as immunity disorders are important elements of electrical, biochemical, genetic, metabolic and immune phenomena that can be associated and correlated.

19. The subclinical risk of early endothelial dysfunction is represented by: increased oxidative stress, early lipoprotein oxidation, conditions leading to immune modifications with metabolic and vascular targets.

20. The triple combination (decreased SOD, increased LDLox and antiLDLox) in young patients with arrhythmias is also predictive for early endothelial dysfunctions in those with dyslipidemia and also, the double association (decreased GPX, increased antiLDLox) in non-dyslipidemic ones.

21. Oxidative stress biomarkers (SOD, GPx, TAS), oxidized-LDL and anti-oxidized-LDL antibodies may adjust and guide the therapeutic management (antioxidants, biological therapy) in young people with arrhythmogenic potential with and without dyslipidemia, in order to achieve the early prophylaxis of severe pathology evolution (atherosclerosis, coronary artery disease).

22. Identification of a decreased level of antioxidants (SOD, GPx, TAS), on genetic background or through other endogenous and/or exogenous factors, favoring molecular and cellular oxidative processes, especially at mitochondrial and nuclear levels, as well as the increased of oxidative modified low density lipoproteins (LDLox) and the corresponding antibodies (antiLDLox), requires assessment of these measurable parameters as biomarkers of subclinical, arrhythmogenic cardiac risk and also, of early vascular endothelial aggression in young people without a pre-existing lesional pathology.

FINAL CONCLUSIONS

Summarizing the general conclusions, the following final conclusions are highlighted:

1. Cardiac arrhythmias in young people, by their multiple clinical aspects, may associate in their pathogenic determinism, subclinical disorders of oxidative stress level and of genetic polymorphisms regarding the major antioxidant systems, with increased oxidative repercussions on plasma lipoproteins, regardless of their level, leading to direct implications, or by their immunogenicity in early endothelial aggression.

2. Biomarkers of oxidative stress, SOD, GPx, TAS recorded decreased levels, the deficits being between half to three quarters of their antioxidant activity, statistically correlated with the cardiac arrhythmogenic potential in young people.

3. In the presence of oxidative stress, argued by diminished antioxidant biomarkers, regardless of LDL value, oxidized-LDL is almost twice increased and by its immunogenicity, leads to an increased amount of anti-oxidized-LDL antibodies (1.5 - 2 times).

4. The mononucleoside profile of SOD2 and iNOS genes outlines the genetic substrate data predisposing to cardiovascular damage, predominantly for the SOD2 heterozygous form AG, as well as for iNOS homozygous form GG.

5. The risk of early endothelial dysfunction in young people with arrhythmias is determined by oxidative stress level, by decrease of antioxidant systems activity, increasing of LDLox and anti-LDLox antibodies, with subintimal deposition potential, especially under hemodynamic variations conditions and vascular immune-inflammatory reactions.

6. Oxidative stress variations are key elements that can couple both cardiac electrochemical arrhythmogenic dysfunction, as well as endothelial dysfunction through lipoprotein oxidation and their immune-pathogenic potential.

7. The value of oxidative stress biomarkers, antioxidant genetic polymorphisms and of immune-metabolic parameters in young people with arrhythmias represents a measurable profile, both for arrhythmogenic and vascular risk, as well for subsequent prophylactic implications and motivation of modern biological therapies.

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