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Oxidative Stress, Endogenous Intoxication and Functional State of Endothelium in Patients with Atrial Fibrillation and Amiodarone-Induced Thyroid Dysfution

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Our study aimed to investigate the role of oxidative stress, endogenous intoxication and endothelial dysfunction in patients with atrial fibrillation treated with amiodarone, particularly in patients with amiodarone-induced thyroid dysfunction. The study involved 70 patients with AF of ischemic origin. After 12 months of amiodarone treatment development of hypothyroidism was found in 20.0% of patients, hyperthyroidism - in 14.0%, and in the majority of patients - euthyroidism. Lipid peroxidation, antioxidant state and endogenous intoxication pointed to the greater oxidative stress and endotoxicosis in patients with amiodarone induced thyroid dysfunction. The functional state of the endothelium, assessed by the level of endothelin-1 and performance of Celermajer test, pointed on reduction of flow-mediated dilation, elevation of serum endothelin-1, which reached the highest levels in patients with amiodarone-induced thyroid dysfunction, mainly hypothyroidism.

Keyword: Atrial Fibrillation, Lipid Peroxidation, Endogenous Intoxication, Endothelial Dysfunction, Amiodarone Induced Hyperthyroidism, Amiodarone Induced Hypothyroidism.

1. Introduction: Atrial fibrillation (AF) is the most common among those cardiac arrhythmias which need treatment. The proportion in Ukraine is close to 1%, it increases with age, reaching 9% in people aged more than 80 years. AF is prognostically unfavorable cardiac arrhythmia, whereas it exacerbates growth in 1.5-2 times of total and cardiovascular mortality, the incidence of chronic heart failure, increases the risk of stroke, is difficult to treat and reduces the quality of life (1, 2).

Among all antiarrhythmic agents of different classes the most effective and most widely used drug for the treatment of AF is amiodarone. However, amiodarone also has effects on the thyroid and other organs (pulmo-, hepato-and neurotoxicity) that may counterbalance its beneficial effects on the heart. The complex effects on the thyroid range from abnormalities of thyroid function tests to overt thyroid dysfunction, either thyrotoxicosis or hypothyroidism (3).

In the pathogenesis of wide range of different nature cardiovascular diseases, including cardiac rhythm and conduction impairment, formation of heart failure, activation of free radical oxidation plays an important role (4). The role of oxidative stress is also clinically and experimentally investigated, as one of the pathogenic mechanisms of iodine-induced thyropathy (5, 6, 7). Thyrocytes constantly produce moderate amounts of reactive oxygen compounds, physiologically required for thyroid hormone synthesis. Nevertheless, when reactive oxygen compounds are over-produced, they may become toxic and damage cell structures and macromolecules including lipids, proteins, and nucleic acids, intensify lipid peroxidation and weaken antioxidant system. Excessive secretion of thyroid hormones is characterized by overactivation of lipid peroxidation and development of endogenous intoxication (8, 9). Some authors propose that deficiency in thyroid hormone synthesis, in particular thyroxine, which has antiradical effect in the body, leads to intensification of lipid peroxidation (9, 10). Strengthening of free radical oxidation processes in patiens with thyropathy may also contribute to hyperlipidemia, excess in blood low-density lipoproteins and middle molecules metabolic disorders. A fundamental component in the pathogenesis of both AF and thyropathy is the predominance of free radicals production over their catabolism, which leads to tissue damage described above.

As well as the common link between heart rhythm disorders of ischemic genesis and iodine-induced thyropathy is endothelial dysfunction, which is based on a progressive vascular lesions (11). There is evidence (12) that the acute use of amiodarone in patients with atherosclerosis improves endothelial function and antioxidant protection. However, there is no information on the state of these systems in the long term. In particular, the functional state of the endothelium in patients with ischemic genesis AF and amiodarone-induced thyroid dysfunction is not studied (13-15).

The goal of this study was to determine the level of oxidative stress, endogenous intoxication and functional state of endothelium in patients with AF of ischemic genesis receiving amiodarone and particularly in patients with amiodaroneinduced thyroid dysfunction.

2. Materials and Methods

Seventy patients (23 women and 47 men) with ischaemic heart disease and atrial fibrillation (permanent and paroxysmal / persistent forms) met the inclusion criteria and gave informed consent, thus being included into this study. The average age of patients was 60.5 ± 1.3 years. The study also included 15 healthy persons as control of normal parameters range. Patients were divided into two groups: Group I - patients who received amiodarone in dose 200 mg daily (in addition to basic therapy - ramipril in mean dose 7.5±0.81 mg daily, verospiron - 50 mg, torasemide - 6.1±0.18 mg, actylsalicylic acid - 75 mg, atorvastatin 15±2.3 mg (n=50); Group II - patients who in addition to basic therapy received digoxin in dose 0.377±0.02 mg weekly and/or bisoprolol 7.25±0.52 mg daily. For all patients of Group I amiodarone was assigned for the first time. The main inclusion criterion was euthyroid condition prior to the assignment of antiarrhythmic therapy.

Endogenous intoxication (EI) was assessed by measuring the level of middle moleculas (MM) in serum using N Gabrielian method, lipid peroxidation primary products - by measuring the level of conjugated dienes (CD) in blood plasma using spectrophotometer method, and final products - malondialdehyde (MDA) using the test with 2-thiobarbituric acid. State of antioxidant defense (AOD) was assesed by determining the activity of ceruloplasmin (CP) in serum using G Babenko method.

To study endothelial function we used non-invasive method of brachial artery flow-mediated dilation (FMD) evaluation. We determined changes in artery diameter in response to increased pressure of blood flow by the method of D. Celermajer et al on the SONOLINE Elegra unit ("Siemens", Germany) with a linear transducer operating frequency of 13 MHz. We measured the initial diameter of the brachial artery. FMD was measured at 90th s after 5 min.

compression of arm by calculating the percentage of change in diameter of the artery compared to the original. Method of carotid artery scanning was used to determine intima-media thickness. Serum endothelin-1 levels were determined using ELISA (Enzo Life Sciences). The investigation was carried out before treatment, after 6 and 12 months of research.

Data were analyzed using GraphPad Prism 6 software (San Diego, CA, USA) and expressed as mean ±S.E.M. A two-sample t-test was used for comparison between two groups, and ANOVA was used for multi-group comparison. $P<0.05$ was considered significant.

3. Results and Discussion

Patients of Ist and IInd groups prior to treatment complained of palpitations, shortness of breath, dizziness, chest discomfort, edema. There were no complaints and objective data related to thyroid dysfunction found in patients before treatment. In all patients after 6 months of treatment, after stabilization of sinus rhythm or achievement of adequate rate control, we observed subjective state improvement, characterized by the disappearance of heartbeat attacks, general discomfort, decreased frequency of angina attacks, reducing the signs of cardiac decompensation after maintenance of sinus rhythm.

Laboratory evaluation of thyroid and pituitary hormones in patients treated with amiodarone have shown manifestation of thyroid dysfunction. After 6 months of treatment hypothyroidism was diagnosed in 6 (12.0%) patients, and after 12 months - in 10 (20.0%) patients. There were no cases of hypothyroidism development found in patients of IInd group. Subclinical amiodarone-induced hypothyroidism (AmIH) was diagnosed in 12% of patients. In the clinical picture there were fatigue (90.0%), dry skin (80.0%), cold intolerance (50.0%), constipation (40.0%), depression (50.0%), bradycardia (60.0 %), edema (80.0%). Thyrotoxicosis was diagnosed in 2 (4.0%) patients after 6 months of treatment with amiodarone, and after 12 months - in 7 (14.0%) patients. In the clinical picture of amiodarone-induced thyrotoxicosis (AmIT) there were irritability in 71.4%, fatigue in 85.7%, tremor of the fingers 85.7%, sweating in 71.4%, tachyarrhythmia 14.3%, ophthalmopathy in 42.8% of patients and, despite receiving amiodarone, recurrence of paroxysmal AF in 36.4%, the deterioration of rate control in 36.4%, progression of heart failure in 71.4% of patients. Most patients (66.0%) remained euthyroid. Consequently, with the development of thyroid dysfunction antiarrhythmic effects of amiodarone decreased or were lost, resulting in deteriorating health, frequent recurrences of paroxysmal AF, progression of heart failure, which all caused the search of possible diagnostic criteria.

Examination of lipid peroxidation state in patients with AF indicate the significant elevation of serum MDA and CD before treatment. In both groups MDA exceeded the level in control and was (5.86 ± 0.32) mcmol / l and (5.97 ± 0.29) mcmol / l in group I and II respectively versus (2.61 ± 0.21) mcmol / l in control ($p<0.001$). Similar results were obtained in the study of CD which were two times increased in patients of both groups in comparison to (0.61±0.02) mcmol/ l in control ($p<0.001$). EI assessment have shown the increase of both middle moleculas classes - peptide (MM_{254}) on 51.65% and 49.76%, and nucleotide (MM_{280}) on 30.3% and 38.38% in Ist and IInd group respectively versus (0,211 ± 0,012) units and (0,297 ± 0,01) units in control group ($p<0.001$). Endogenous intoxication decreased nucleotide-peptide index. Dysfunction of antioxidant defense system manifested with increased activity of ceruloplasmin ($p <0.001$) in both groups compared to control (Table 1). Analysis of the FMD assessment and evaluation of endothelin-1 demonstrated severe endothelial dysfunction in patients with AF (Table 2). Before treatment FMD proved to be reduced in patients of groups I and II on 46.71% and 46.35%, respectively, compared with 13.85% in control ($p<0.001$). There also was a trend toward higher endothelin-1 levels in patients of Ist and IInd group (5.91 ± 1.51) pg/ml ($p<0.001$) and (6.22 ± 1.08) pg/ml ($p<0.001$), respectively versus (3.04 ± 0.86) pg / ml in control.

Under the influence of basic therapy received by patients of IInd group no significant changes of lipid peroxidation, AOD, EI and endothelial function were observed (p>0.05). However, in patients of the Ist group after 6 months of amiodarone treatment a tendency to deterioration of lipid peroxidation and AOD parameters have revealed (Fig. 1). As can be seen from Table 1 there also was a trend to an increase of EI parameters (p>0.05). After 12 months of amiodarone treatment MDA levels increased already on 15,04% (p<0.01), CD on 12.1% (p<0.01), CP on 18.02% (p<0.001), MM_{254} on 17.81% (p<0.01), MM_{280} on 17, 0% (p<0.01) in comparison with before treatment levels.

Table 1 Dynamics of middle moleculas in patients of Group I and Group II during treatment

Index	Control	Group I (n=50)			Group II (n =20)		
		before treatment	after treatment		before treatment	after treatment	
			6 mon.	12 mon.		6 mon.	12 mon.
MM_{254}, units	0,211± 0,012	0,320± 0,01*	0,351± 0,01*	0,377± 0,008*,ǂ	0,316± 0,01*	0,309± 0,01*	0,300± 0,01*
MM_{280}, units	0,297± 0,01	0,412± 0,015*	0,456± 0,01*	0,482± 0,009*,ǂ	0,411± 0,012*	0,396± 0,01*	0,387± 0,01*
MM_{280}/MM_{254}	1,41± 0,014	1,29± 0,013*	1,29± 0,011*	1,27± 0,01*	1,30± 0,012*	1,28± 0,01*	1,29± 0,01*

Values are expressed as mean ±S.E.M. *P<0.001 versus control. ǂP<0,01 versus before treatment.

There also was a tendency to progression of endothelial dysfunction in patients of the Ist group already after 6 months of amiodarone treatment, which manifested in the reduction of FMD on 17.2% and growth of intima-media thickness on 3.22% in comparison with the levels of these parameters before treatment (p>0.05). After 12 months of treatment FMD decreased already on 28.72% (p<0.001), the intima media thickness has increased on 8.06% (p<0.001) versus level of these indicators before treatment. We also observed a steady increase of endothelin-1 levels on 24.87% (p<0.05) after 6 months and on 39.42% (p<0.001) after 12 months of amiodarone treatment (Fig. 2), which was not seen in patients of IInd group (p>0.05).

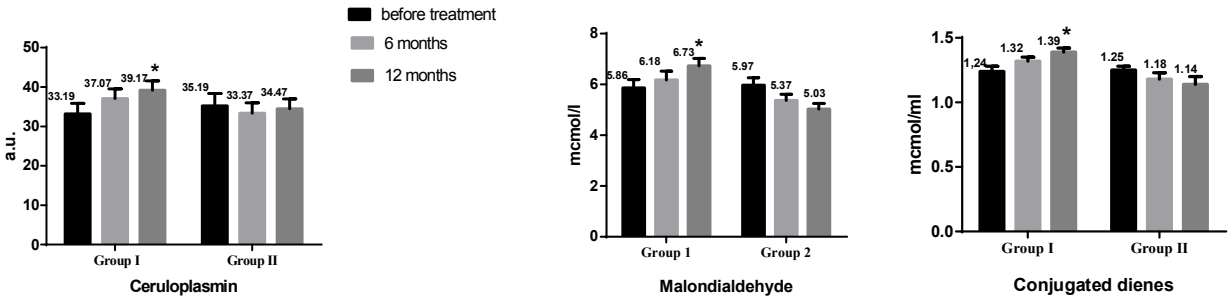

Figure 1 Dynamics of malondialdehyde, conjugated dienes and ceruloplasmin in patients of Group I and Group II during treatment. P<0.05 versus before treatment

Table 2 Dynamics of brachial artery flow-mediated dilation evaluation in patients of Group I and Group II during treatment

Index	Control	Group I (n=50)			Group II (n =20)		
		Before Treatment	After Treatment		Before Treatment	After Treatment	
			6 mon.	12 mon.		6 mon.	12 mon.
Initial brachial artery diameter (D), mm	3.60±0,54	4,55± 0,60*	5,04± 0,57*	5,23± 0,55*,ǂ	4,50± 0,59*	4,60± 0,51*	4,58± 0,44*
FMD %	13,85±1,83	7,38± 1,56*	6,11± 1,68*	5,26± 0,95*,ǂ	7,43± 1,89*	7,30± 2,09*	7,39± 1,95*
Intima-media, mm	0,55±0,02	0,62± 0,03*	0,64 ±0,03*	0,67 ±0,03*,ǂ	0,61± 0,02*	0,63± 0,02*	0,60± 0,02*

Values are expressed as mean ±S.E.M. *P<0.001 versus control. ǂP<0,01 versus before treatment.

For analysis of lipid peroxidation, antioxidant defence state, endogenous intoxication and endothelial function depending on thyroid function in patients with AF who received amiodarone 3 groups were formed: patients with euthyroidism, AmIH and AmIT (Table 3). Comparison of the investigated parameters depending on the condition of thyroid indicates that they were significally worse in patients with hypothyroidism (p<0.05), and thyrotoxicosis (p<0.05) than in patients with euthyroidism.

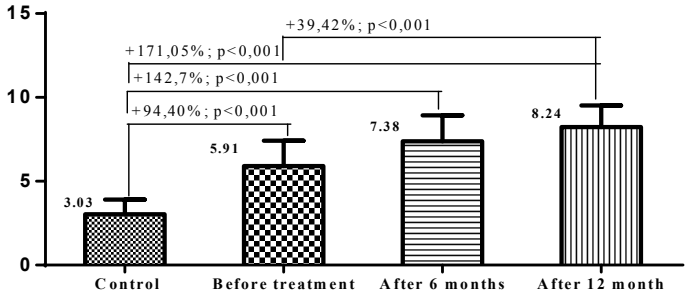

Figure 2: Dynamics of endothelin-1 in patients treated with amiodarone

Table 3: Indicators of lipid peroxidation, antioxidant defens, endogenous intoxication and endothelial function in patients depending on the functional state of thyroid gland

Index	Group I (n=50)		
	Euthyroid (n =33)	AmIH (n =10)	AmIT (n =7)
Malondialdehyde, mcmol/l	5,95±0,26	7,02±0,32*	7,11±0,28*
Conjugated dienes, mcmol/l	1,32±0,02	1,48±0,02ǂ	1,40±0,02*
Ceruloplasmin, a.u.	36,25±1,12	40,73±1,03*	38,45±0,95
MM_{254}, a.u.	0,329±0,013	0,398±0,01*	0,389±0,01*
MM_{280}, a.u.	0,434±0,01	0,502±0,009*	0,494±0,01*
MM_{280}/MM_{254}	1,32	1,26	1,27
FMD, %	5,84±0,93	4,25±0,57*	5,15±0,45
Intima- media, mm	0,63±0,03	0,68±0,02*	0,64±0,02
Endothelin-1, pg/ml	7,02±1,20	9,07±0,43*	7,2± 1,09

Values are expressed as mean ±S.E.M. *P<0.05 versus euthyroid. ǂP<0,01 versus euthyroid.

4. Conclusions

1. Amiodarone admission for 12 months by patients with AF provoked intensification of free radical oxidation stress and antioxidant defence reduction, growth of endogenous intoxication, especially in patients with amiodarone-induced thyroid dysfunction.
2. The progression of endothelial dysfunction, which manifested in reduced FMD, increased thickness of intima-media complex, higher serum endothelin-1 was observed in patients treated with amiodarone. The most pronounced changes in these parameters were seen in patients with amiodarone-induced thyroid dysfunction, mainly hypothyroidism.

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