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Primary prevention of atrial fibrillation with the correction of its potentially modifiable risk factors in comorbid patients with abdominal obesity. Prospective study

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Abstract

Objective. To assess the role of the improvement of potentially modifiable risk factors (RF) for the primary development of atrial fibrillation (AF) in comorbid patients with abdominal obesity (AO) and atrial premature complexes (APCs) with high risk of the development of this arrythmia.

Materials and methods. The study included 489 patients with AO and APCs aged from 58 to 72 years (67,9 ± 0,7 years on average). After the examination, a 3-year prog-

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nostic time range for the development of AF was established for all patients. All study participants underwent the correction of potentially modifiable risk factors of AF (body mass, blood pressure, glucose and blood lipid levels, etc.) until target values have been reached, as well as smoking cessation, physical activity, etc. The study endpoint was the sinus rhythm preservation or AF manifestation.

Results. All study participants were divided into two groups. Group 1 included 278 (56,85 %) patients with insufficient RF correction, group 2 included 95 (19,43 %) patients who achieved target values of all potentially modifiable RFs of AF. Patients without RF correction were included into the control group. Studied groups did not differ significantly by sex, age, comorbid diseases, risk factors for the development of AF.

Patients from all groups did not differ significantly by the incidence of AF (paroxysmal and persistent forms) during the first year of follow-up, and had AF in 92.68 %, 85.29 % and 93.54 % of cases, respectively. Patients from group 2, who maintained the achieved target values of potentially modifiable RFs for 2 years or more, had 57.58 % and 14.29 % actual and predicted AF development ratio during the 2nd and 3rd year of observation, respectively.

Conclusion. The decrease of actual AF compared to predicted AF was observed only in patients with AO and APCs with complex correction of all potentially modifiable AF RFs who reached RF's target values and maintained them for over 2 years.

Keywords: atrial fibrillation, primary prevention, correction of potentially modifiable risk factors.

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Introduction

The combination of abdominal obesity (AO), arterial hypertension (AH), diabetes mellitus (DM), dyslipidemia, hypodynamia increase "cardiometabolic" risk of various cardiovascular diseases, including atrial fibrillation (AF) [1, 2]. The main causes of AF development in comorbid patients with AO are the intracardiac hemodynamic disorders, in particular, left ventricular dysfunction, atrial dilatation, etc. Moreover, profibrogenic inflammatory mediators (galectin-3, transforming growth factor β1, etc.) due to the increase in epicardial fatty tissue may also affect myocardium [3–5]. In recent years, using the model of dynamic observation of comorbid patients with AO, including the analysis of signal-averaged ECG parameters, dispersion of P(Pd) wave, the number and the type of atrial premature complexes (APCs), researchers identified patients with high 3-year risk of development of primary AF as well as assessed probable time range of its manifestation [5].

Risk change of primary AF development after the correction of separate potentially modifiable factors is well studied by using the various risk-stratification models in comorbid patients with AO without APC registration [6]. However, data on the effect of complex correction of potentially modifiable risk factors (RF) of AF on its primary development in comorbid patients with AO and CHD with the assessment of potential prognostic time interval of this arrhythmia development in the literature is scarce.

The aim of the study was to determine the role of complex correction of potentially modifiable RF of AF formation on its manifestation in comorbid patients with AO and APC with high risk of this arrhythmia development.

Methods

The study included 489 patients with AO and APCs aged between 58 and 72 years (mean 67.9 ± 0.7 years). The number of males and females was 198 (40.49 %) and 291 (59.51 %), respectively ($p > 0.05$). AH was detected in 415 (84.87 %) patients, DM in 328 (67.08 %), chronic obstructive pulmonary disease in 109 (22.29 %), hyperlipidemia in 427 (87.32 %), tobacco smoking in 334 (68.30 %), hypodynamia in 409 (83.64 %).

All patients after clinical-laboratory examination, echocardiographic examination, daily ECG monitoring, registration of signal-averaged ECG, etc. were

subjected to inclusion criteria. Methods and hardware for determination of left ventricular contractility and dysfunction, cardiac chamber volumes, as well as filtered P-wave duration of signal-averaged ECG (FiP-P), Pd, prognostic index of AF (PI) were described earlier [5]. The diagnosis of AO, body mass index (BMI), hypodynamia, functional class of heart failure (6-minute test), mean BP was performed according to generally accepted criteria [1, 2].

Based on atrial ectopy analysis, PI was calculated according to the formula:

$$PI = (A \div B) \times (C \div N),$$

where PI is the prognostic index of AF development, A and B are the duration of FiP-P and Pd determined by signal-averaged atrial ECG and daily ECG monitoring data, respectively (in m/s). C is the linear deviation of the corrected coupling interval in more than 20 APCs, N is the number APCs used for the study, expressed as number/hour [5].

The three-year risk of primary AF was determined at PI ⩽ 8 points. The PI was subsequently assessed at follow-up intervals of 1–3 months. If the PI decreased from baseline and at follow-up, the x prognostic time range for AF (PPTRAF) was calculated (in months) according to the formula:

$$PPTRAF = [PI_1 - 0.01] \div [PI_1 - (PI_2, PI_3, \text{etc.})] \times I,$$

where, PPTRAF is the potential prognostic time range of AF development. PI_1 — PI values after the first examination, PI_2, PI_3, etc. — PI_2, PI_3 values in 2–3 and subsequent studies respectively, 0.01 — PI values at which spontaneous episodes occur, I — interval in months between first and subsequent (2–3 etc.) studies [5]. Then the calculated PPTRAF was compared with the actual development of AF.

The inclusion criteria were: presence of sinus rhythm, detection of ⩾ 100 APCs per day of the follow-up [2, 7], chronic heart failure of I–II functional class according to NYHA, absence of AF registration with at least 4–5 procedures of 24–72 hour ECG monitoring at least once in 1–2 weeks for 2–3 months, with preserved left ventricular ejection fraction (LVEF) (⩾ 54 %) [2, 7], 3-year risk of development of AF with determination of PPTRAF [5], informed consent from the patient to participate into the study. The study was approved by a local ethics committee.

Patients with myocarditis, cardiomyopathies, Wolff-Parkinson-White syndrome, malformations, various clinical forms of coronary heart disease and alcohol abuse were excluded from the study.

All patients were offered the correction of AF potentially modifiable RF. The targeted correction values of modifiable factors were: reduction of BMI < 25 kg/m^2 and/or waist circumference ⩽ 80 cm and ⩽ 94 cm in women and men, respectively, BP ⩽ 139/89 mm Hg, but not below 130/80 mm Hg. [1], plasma total cholesterol and triglycerides ⩽ 5.2 mmol/L and ⩽ 1.7 mmol/L, respectively; plasma low-density lipoprotein cholesterol ⩽ 1.4 mmol/L; fasting blood glucose ⩽ 5.8 mmol/l, increased high-density plasma lipoprotein cholesterol ⩾ 1.0 mmol/l in men and ⩾ 1.2 mmol/l in women [1]. All patients were advised to eat a healthy diet, regular aerobic physical activity (150 minutes or more per week), to quit smoking. Hypotensive drugs (indapamide, telmisartan, valsartan, etc.) were used to normalize BP. Hypoglycemic and hypolipidemic drugs (metformin, empagliflozin, liraglutide, statins, as well as diet, etc.) were used to normalize blood glucose and lipids levels [1]. No antiarrhythmic drugs were used to reduce APCs. When the subjective sensation of atrial ectopy appeared, sedatives, potassium drugs (combination of potassium asparaginate and magnesium asparaginate, etc.) were recommended.

Assessment of the effectiveness of potentially modifiable RFs correction on AF development was determined (in points) according to the formula: K ×D, where K is equal to "0" and "1" in absence and incomplete correction (not achieving the target values) respectively, "2" in case achieving the target values of predictors of this arrhythmia (in units). D is the duration of corrected RFs retention after their modification (in months).

Patients were followed up for up to 3 years. A registration of AF or the maintenance of the sinus rhythm was the end point of the study. All investigations, including daily ECG monitoring, PI determination, PPTRAF calculation were performed on sinus rhythm at least once in 2–3 months, ECG registration — once a month. Nursing staff monitored BMI, waist circumference, BP, fasting blood glucose. The patients themselves performed regular monitoring of heart rate and blood pressure at least twice a day, using household tonometers. If an irregular heart rate was detected, an ECG was recorded on a smartphone or by contacting the family doctor's office, polyclinic, etc.

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[2]. The episode of AF was the reason for prescribing anticoagulants (dabigatran, rivaroxaban, etc.) [2]. When this arrhythmia occurred, all studies were performed after the resolution of the first episode, and in the case of pharmacological cardioversion, after 5–7 half-lives of the antiarrhythmic drugs used for its elimination.

The study was conducted in accordance with Good Clinical Practice and the principles of the Declaration of Helsinki.

Statistical analysis

Mean values as well as the error of the mean values (M ± m), standard deviation (σ), 95% CI of the mean values, Student's t test, X^2 test were used for statistical processing of the obtained data, $p < 0,05$ values were taken as statistically significant difference of the values. The normality of the distribution of the quantitative variables was assessed using the Kolmogorov-Smirnov test and the ±3σ rule (Gaussian distribution). Pearson and Spearman linear and rank correlation (r) were used (for nonparametric variables) respectively, and the comparison between two binary variables was assessed by using logistic regression with odds ratio (OR) in version 11.0 of «Statistica» computer software.

Results

After the inclusion in the study, all patients had a decrease in PI from baseline and at follow-up, due to a decrease in the duration of the APCs coupling interval and its variability (OR = 8.2), an increase in Pd (OR = 6.9) and the number of extrasystoles (OR = 0.91).

All patients, depending on the correction degree of the potentially modifiable RFs of AF development, were divided into two groups. The first group consisted of 278 (56,85%) patients with incomplete correction, the second group included 95 (19,43%) patients with the achievement of the target values of all potentially modifiable RFs, including those due to dietary compliance, regular aerobic physical activity, tobacco cessation. The control group included the remaining patients without correction of modifiable AF predictors.

At baseline, a statistically significantly shorter duration of AF registration before the correction was detected in the second group patients compared to the first and control groups, while the other studied parameters did not differ significantly (Tables 1, 2).

Table 1. **Status of clinical and instrumental parameters, PPTRAF in patients from groups I and II at baseline[1]**

Parameters	Control group n = 116	I group n = 278	II group n = 95
Age, years	66,8 ± 0,63 (58,6–74,5)	65,9 ± 0,36 (59,7–73,6)	65,9 ± 0,8 (57,7–69,8)
BMI, kg/m^2	36,5 ± 0,48 (30,8–43,7)	36,8 ± 0,32 (30,4–42,8)	35,8 ± 0,42 (31,5–39,4)
Waist circumference, cm	128,2 ± 1,5 (106–149)	129,8 ± 1,1 (109–151)	130,2 ± 1,9 (105–148)
Blood glucose, mmol/l	9,3 ± 0,4 (6,4–14,4)	9,3 ± 0,26 (6,6–13,8)	8,8 ± 0,8 (6,8–14,9)
Total cholesterol, mmol/l	7,8 ± 0,1 (6,1–9,8)	8,0 ± 0,1 (6,5–10,9)	8,2 ± 0,2 (6,4–9,9)
Low density lipoprotein cholesterol, mmol/l	4,7 ± 0,2 (3,6–5,9)	4,9 ± 0,1 (3,6–6,1)	4,5 ± 0,2 (3,2–5,6)
High density lipoprotein cholesterol, mmol/l	1,1 ± 0,1 (0,8–1,5)	0,9 ± 0,1 (0,7–1,6)	1,1 ± 0,5 (0,8–1,4)
Triglyceides, mmol/l	2,5 ± 0,1 (1,6–3,5)	2,3 ± 0,1 (1,3–3,6)	2,6 ± 0,2 (1,7–4,4)
AO duration before correction, years	39,3 ± 0,8 (29–52)	38,7 ± 0,8 (27–54)	14,1 ± 1,1*◊ (8–20)
PPTRAF, months	34,6 ± 2,1 (4–59)	35,2 ± 1,3 (6–58)	22,9 ± 1,2 (5–36)

Comment. 1 – up M ± m, down – 95% CI mean values,
* – statistically significant difference in parameters when comparing with the control group,
◊ – II group in comparison to the I group (at $p < 0,05$).

There was no significant difference in gender, age, frequency of hypertension, DM, chronic obstructive pulmonary disease, tobacco smoking, and hypodynamia between patients from the first and second groups, either among themselves or in comparison with controls.

In 164 (58,99%), 34 (35,79%), 62 (53,45%) patients from the first, second and control groups respectively, PPTRAF was 6–12 months ($p > 0,05$), in 56 (20,14%), 33 (34,74%), 36 (31,03%) 13–24 months ($p > 0,05$), and in the remaining patients of these groups — 25 to 36 months ($p > 0,05$).

In 94 (33.81%) and 28 (29.47%) patients of the first and second groups the maintenance of the achieved indices was kept for 12 months, in 88 (31.65%) and 29 (30.53%) — for 12–23 months, and in the remaining patients of these groups — for more than 24 months. The achievement of the target values of potentially modifiable RF and their maintenance for more than 2 years from the start of correction correlated with the duration of AF registration before the correction for less than 15 years (OR = 12, 8), performing regular aerobic physical activity (OR = 10.9), dietary compliance (OR = 8.5), use of a glucagon-like peptide-1 receptor agonist (liraglutide) (OR = 5.4), empagliflozin (OR = 2.4).

Table 2. **Status of clinical and instrumental parameters in patients from groups I and II at baseline (A) and at the end of the predicted period of AF development or at its onset (B)[1]**

Group	Control group n = 116		I group n = 278		II group n = 95	
Parameter	A	B	A	B	A	B
LV EF, %	61,84 ± 0,67 (54–69)	54,01 ± 0,68* (46–62)	61,54 ± 0,32 (55–68)	60,38 ± 0,35 (52–70)	61,47 ± 0,89 (54–68)	68,35 ± 0,91* (59–77)
E/A, units	0,95 ± 0,02 (0,71–1,23)	0,78 ± 0,01* (0,61–0,95)	0,94 ± 0,01 (0,75–1,15)	0,96 ± 0,01 (0,84–1,08)	0,94 ± 0,01 (0,74–1,15)	1,07 ± 0,01* (0,92–1,21)
LAEDD index, ml/m^2	31,78 ± 0,25 (28–33)	37,93 ± 0,57* (31–41)	31,54 ± 0,24 (29–35)	35,84 ± 0,23* (30–39)	31,43 ± 0,25 (28–34)	25,32 ± 0,43* (22–29)
Amount of APC per hour	374 ± 6 (301–446)	597 ± 22* (324–876)	384 ± 3 (311–467)	376 ± 8 (188–559)	384 ± 11 (297–462)	234 ± 16* (132–307)
Mean BP, mmHg	117,1 ± 1,2 (103–131)	108,7 ± 0,9* (97–121)	118,1 ± 0,7 (102–132)	107,8 ± 0,5* (96–119)	118,9 ± 1,4 (104–131)	105,2 ± 1,3* (95–116)
6-minute walking test, meters	436,5 ± 6,7 (365–510)	375,7 ± 5,1* (315–436)	447,9 ± 6,3 (372–516)	442,7 ± 6,7 (368–518)	422,9 ± 7,3 (358–489)	546,5 ± 9,8* (445–648)

Comment. 1 — up M ± m, down – 95 % CI mean values
* — II group in comparison to the I group (at p < 0,05).

In patients from the control and first groups, the ratio (in %) of actual to predicted development of first AF episodes was 87.93% and 88.13%, respectively (p > 0.05), whereas in second group it was 54.74% (p < 0.05) (Table 3). In all patients from the first, second and control groups, the incidence of AF did not differ significantly during the first two years of follow-up after inclusion in the study (see Table 3). In patients from the second group, at maintenance of the reached target values of potentially modifiable RFs for more than 1 year, the ratio of actual AF development to the predicted one in the 2nd and 3rd years of follow-up was 57.58% and 14.29% respectively (see Table 3). No lethal outcome, myocardial infarction, stroke or other complications were observed in the above-mentioned patients.

For the patients in the control group, a significant decrease in LV EF, E/A ratio, mean BP, 6-minute test performance and a statistically significant increase in the number of APCs and Left atrium end-diastolic dimension (LAEDD) index were observed by the end of the predicted period of AF development or at its onset. On the other hand, only a significant decrease in mean BP was found in the first group of patients, while other parameters in these groups compared with baseline data did not change significantly (see Table 2). A statistically significant decrease in mean BP, LAEDD index, the number of APCs, as well as significant increase in LV EF, E/A, and the 6-minute test were observed in patients from the second group, compared with the baseline (Table 2).

Discussion

Currently, there are various predictors of AF development, such as: left atrial dilatation, decreased LV EF, deterioration of transmitral flow, detection of APC, abnormal values of signal-averaged ECG, Pd, etc. [8]. For the early diagnosis of AF in all patients, especially over 65 years old when identifying predictors of its development or thromboembolic complications, it is recommended to assess pulse regularity by the principle of "pulse-screening-test", determining both palpation and by using household tonometers, followed, if necessary, by ECG registration on a smartphone

Table 3. **Effect of the potentially modifiable AF RFs correction on the development of the first attacks of this arrhythmia in groups I and II[1]**

Duration of the follow-up after the inclusion into the study	Control group n = 116	I group n = 278	II group n = 95
From 6 to 12 months	58/62 (93,54 %)	150/164 (92,68 %)	29/34 (85,29 %)
From 13 to 24 months	29/36 (80,56 %)	47/56 (83,93 %)	19/33(57,58 %)*◊
From 25 to 36 months	15/18 (83,33 %)	48/58 (82,76 %)	4/28 (14,29 %)*◊
Total	102/116 (87,93 %)	245/278 (88,13 %)	52/95(54,74 %)*◊

Comment. 1 – numerator — actual AF development rate, denominator — projected PPTRAF, % — ratio of actual to projected AF development rate over the observation period;
* – statistically significant difference in parameters when comparing with the control group,
◊ – II group in comparison to the I group (at p < 0,05).

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or when contacting medical institutions [2]. At least 25 risk-stratifications have been proposed to assess the risk of primary AF development in comorbid patients, with a five-year predictive accuracy averaging between 20 % and 50 % [6]. However, risk-stratifications and predictors of AF development determine the presence of potential risk without definition of concrete terms of its realization. In recent years, sporadic work on specific timing of PPTRAF registration, based on a model of dynamic patient follow-up, has appeared [5].

A total of 489 comorbid patients with AO and APC aged between 58 and 72 years (mean, 67.9 ± 0.7 years) were followed up.

The "obesity paradox" is observed in patients with excessive BMI: patients with AO have a minimum probability of mortality due to various cardiovascular diseases and their complications [2]. Similar data were obtained in the present study.

It is now known that atrial ectopy due to the trigger mechanisms, such as delayed postdepolarization, is usually associated with the hyperpolarization of cell membranes of cardiomyocytes within 60–70 mV, which indirectly reflects potentially reversible nature of their dysfunction. Its induction may be the result of stress, vegetative or electrolyte imbalance, etc., and after the cause elimination, APCs usually stop [8]. In most cases, APCs due to the development of these mechanisms are regarded as supraventricular ectopias with a favorable prognosis, usually not requiring the use of the antiarrhythmic therapy, except for the presence of a subjective sense of extrasystole [2, 8]. Meanwhile, further hyperpolarisation of myocardiocyte membranes, e.g. between 50–60 mV, is associated with a local delay in the spread of excitation with Wenckebach phenomena and the formation of unidirectional conduction block in this area, leading to a persistent re-entry loop and/or an ectopic focus. The occurrence of this mechanism is associated with deeper metabolic abnormalities and/or as a result of organic myocardial damage such as inflammation [8]. Persistent and/or recurrent supraventricular extrasystole caused by these mechanisms can independently or indirectly induce the development of myocardial areas with irregular refractoriness, causing the formation of atrial substrate, predisposing to the appearance of primary AF as well as "atrial arrhythmogenic cardiomyopathy" [2, 8–11].

In our study, after determining the 3-year risk of AF development in comorbid patients with AO and APC, PPTRAF was calculated at least once every 2–3 months at decreasing PI over the course of follow-up. The decrease in PI values from baseline and at follow-up was due to decreased variability of the APC clutch interval, increased Pd and, to a lesser extent, the number of extrasystoles, which probably reflects the formation of AF substrate [10, 11]. It should be noted that the low variability of the APC coupling interval is indirectly confirmed by "re-entry" mechanisms and/or the formation of a pathological ectopic focus, while high values of this index show the presence of trigger mechanisms [8, 10, 11].

According to the obtained data, in 89.31 % of comorbid patients with AO and APC, despite the recommendations to implement a "healthy lifestyle", there was virtually no or incomplete correction of all potentially modifiable RFs of AF development, while in the rest — correctable predictors reached the target values. The maintenance of the target values of potentially modifiable RFs for 2 or more years correlated mainly with the duration of AF registration before the correction for less than 15 years and, to a lesser extent, with regular aerobic physical activity, dietary compliance and the use of the hypoglycemic agents (glucagon-like peptide-1 receptor agonist and empagliflozin).

The results of the study showed that the ratio (in %) of actual to predicted development of the first AF episodes in patients with and without incomplete correction of RFs did not differ significantly and was 87.93 % and 88.13 %, respectively.

During the first year of follow-up, the incidence of this arrhythmia was not significantly different in comorbid patients with AO with maintained target values of potentially modifiable RFs and in patients without or with incomplete correction of RFs: 85.29 %, 93.54 % and 92.68 %, respectively.

In comorbid patients with AO and APC, the ratio of actual to predicted occurrence of AF during the second and third year of follow-up was 57.58 % and 14.29 %, respectively, when target values of potentially modifiable RFs were maintained for 2 years and longer.

In comorbid patients with AO and APC, the "delayed effect" of correction of potentially modifiable RFs, manifesting in the 2nd and 3rd year of follow-up after reaching their target values, is probably be-

cause APCs may have been registered indefinitely before study inclusion. That may induced the appearance of atrial myocardial zones with conduction and refractoriness variability and/or the formation of multiple ectopic foci [7, 9]. Other contributing factors include the fact that patients with AO have a rather slow regression of excess epicardial adipose tissue, and a prolonged effect of the glucagon-like peptide-1 receptor agonist (liraglutide), empagliflozin, lead to a reduction in the release of profibrogenic inflammatory mediators from epicardial adipose tissue products in comorbid patients with DM and AO [4, 12].

All patients with AO have indications for the complex correction of potentially modifiable RFs of AF development, reaching target values, as well as lifestyle modification, including dietary compliance, regular aerobic physical activity, tobacco cessation, etc. According to the data obtained, in 12.47% of comorbid patients with AO and APC, a positive effect of potentially modifiable RFs correction was observed in case of the maintenance of target values for 2 years and more. The choice of therapy used for the primary prevention of AF in this category of patients, especially with no or incomplete correction of potentially modifiable RFs, is a subject for further study. When a 3-year PPTRAF is detected, the antiarrhythmic pharmacotherapy may be the method of choice as the primary prevention of this arrhythmia in comorbid patients with AO and APC without or with the incomplete correction of potentially modifiable RF [7, 13, 14]. However, in these patients, with long-term antiarrhythmic drugs, the potential risk of adverse events may exceed the predicted benefit of treatment [7, 14]. On the other hand, if the 3-year PPTRAF is detected, the use of pharmacological antiarrhythmic therapy, represented by beta-adrenoblockers or by another kind of treatment, is most likely indicated for the primary AF prevention in comorbid patients with AO and APC, who managed to maintain the target values of potentially modifiable RF, during the first year of follow-up [7, 13].

Subsequently, one year later, continuation of antiarrhythmic therapy, while maintaining the target corrected values, in these patients seems to depend on the assessment of PPTRAF.

Conclusion

In comorbid patients with AO, APC and 3-year PPTRAF, a decrease in the primary AF development was observed only in patients with comprehensive correction of all potentially modifiable RFs and only if the target values were maintained for 2 or more years. The achievement of the target values of potentially modifiable RFs mainly correlated with the duration of AO before correction for less than 15 years and to a lesser extent — with regular aerobic physical activity and dietary compliance.

Conflict of interest. None declared.

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