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Estimation of atrial fibrillation risk development in patients with metabolic syndrome during atrial extrasystole registration

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Summary

Objective

To estimate atrial fibrillation (AF) risk development in order to determine its long-term and short-term development risks in patients with metabolic syndrome (MS) during atrial extrasystole (AE) registration according with performed prospective study

Materials and methods

1427 patients of the age between 45 and 75 years with MS and registered AE were observed from 1998 to 2012. Apart of general examination, patients underwent hemodynamic monitoring, atrial late potential (ALP) and P-wave dispersion (Pd) measurement and estimation of AE character with quantification of AF development risk index

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(AFDRI). After inclusion into the study patients were observed during the period from 1 to 4-5 years. Presence or absence of AF development during the period of observation was considered the endpoint of this study.

Results

156 (10,93%) of examined patients developed paroxysmal or persistent form of AF during 4–4.5 years of prospective observation. Atrial dilatation and/or ALP detection after single examination in patients above 55 years with MS determine long-term risk of AF development. Short-term risk (during 1–2 years after the first examination) of AF development can be estimated just after dynamic observation of patients: AFDRI reduction to 35% and more during each 3–4 month of observation comparing with initial results determines AF development in patients with MS during 1–2 years, and if AFDRI levels are less than 0,5 units with subsequent reduction to 70% and more each 1–3 months, it determines AF development during 6 months after examination.

Conclusions

Complex examination of MS patients that includes ALP and Pd measurement and AFDRI estimation allows to determine both long-term and short-term risks of AF development.

Keywords

Atrial fibrillation, metabolic syndrome, development risk identification

Indtroduction

Metabolic syndrome (MS) is mentioned as one of atrial fibrillation (AF) frequent causes in international and Russian guidelines for AF treatment. It is recommended to perform pulse screening in patients older than 65 years and in case of irregular pulse make electrocardiogram (ECG) registration to verify the diagnosis [1,2]. During the last years such predictors of AF development like left atrium dilation, mitral valve calcinosis, left ventricular ejection fraction reduction (LVEF), transmitral flow parameters worsening, the presence of atrial late potentials (ALP), increased P-wave dispersion (Pd), etc have been determined [1, 2, 3, 4]. But we were unable to find in available literature an example of prospective study with complex use of ALP, Pd together with the identification of atrial extrasystoles (AE) character aiming to estimate the risk of AF development in patients with MS.

The objective of this work is to estimate AF predictors use for determining long-term and short-term development risks in patients with MS based on performed prospective study.

Materials and methods

1427 patients between 45-75 years (average age 66,3±2,7 years) with MS were observed during the period from 1998 to 2012. MS diagnosis was based on common criteria [3]. The following inclusion criteria were chosen: the presence of sinus rhythm, pathological amount of AE (more than 50 extrasystoles per day) [3] registration, chronic heart failure, I-II NYHA class, no AF registration after 2-3 repeats of 1-3 days of 24 hours ECG monitoring, signed informed consent. Patients with acute coronary syndrome, WPW syndrome, sick sinus syndrome, atrioventricular heart block, artificial cardiac pacemaker, ventricular tachycardia and extrasystoles (II-V classes according with the classification of Rayn), valvular defects, cardiomyopathies, thyroid gland dysfunction, uncontrolled arterial hypertension, severe somatic diseases that could have influenced the results and also patients with LVEF less than 45%, left ventricle aneurism, chronic heart failure III-IV NYHA class [3] were excluded from the study. Essential hypertension was found in 1133 patients (79,40%), 245 patients (17,39%) had the history of myocardial infarction, 914 (64,05%) had diabetes mellitus, 216(15,14%) had chronic bronchitis.

Apart of clinical examination patients underwent the examination of central and intracardiac hemodynamics using echocardiograph Hitachi-EUB-5500 and Doppler-echocardiography according with the common techniques. and such hemodynamic characteristics like LVEF, final diastolic volume of left atrium (laFDV), and the volume more than 28 mL/m^2 was considered as LA dilation [3, 5], left ventricular mass index (LVMI), E (early) and A (late) left ventricle filling velocities and E/A ratio (E/A ratio less than 1,0 was considered as diastolic dysfunction [5]) were determined or quantified for each patient. Determination of signal-averaged ECG characteristics like filtered P-wave duration (FiP-P), duration of signals in the end of P-wave weaker than 5 μV (D_s) and root mean-square amplitude of 20 ms of P-wave (RMS-20), Pd, FiP-P/Pd ratio expressed in relative units have been previously described [6].

All patients received basis hypotensive therapy with angiotensin-converting enzyme inhibitors (enalapril (ednit, renitec, etc)), saluretics (indapamide (arifon), etc) including all patients who survived myocardial infarction, and controlled glucose and lipids concentrations in blood using diet or glucose- and lipid-lowering drugs like statins. In all patients we quantified the risk of AF development index (AFDRI) using formula AFDR=(FiP-P/Pd)*(A/B), where AFDRI is atrial fibrillation development risk index, FiP-P – filtered P-wave duration(ms) in signal-averaged ECG , Pd – P-wave dispersion(ms), determined as the difference between maximal and minimal values of P-wave duration during standard 12-lead ECG registration, A – linear deviation (LD) of corrected pre-ectopic interval (PEIcor) not less than in 20 AE, B – the number of AE used for this study expressed as amount of extrasystoles per 1 hour [7]. PEIcor estimation using not less than 20 extrasystoles excludes false-positive results [8]. It is worth to mention that we used transesophageal ECG registration in case of frequent AE to visualize P-wave more precisely especially when it was difficult to distinguish or it was mixed with T-wave.

After inclusion in the study patients have been observed during the period from 1 to 4-5 years. Presence or absence of AF development during this period was considered as the endpoint of the study. All examinations including ECG monitoring were performed not less frequently than once per 3-4 months, control of patient's state and ECG registrations were done every month. Regular blood pressure and heart rate control were independently measured by patients.

Statistical analysis of results was performed using Student's t-test, χ^2, odds ratio (OR), confidence interval (CI)of mean values and OR and "Statistica 11.0" software.

Results and discussion

After inclusion into the study 156 (10,93%) of 1427 patients demonstrated development of paroxysmal or persistent AF form during 1-4 years of observation. All patients were divided into 2 groups. The first group (I group) included 1271 (89,07%) patients who haven't developed AF, all other patients who acquired AF during the period of prospective observation were included into the second group (group II). 8 patients of the second group (5,13%) underwent examination 3-6 months before they developed AF, 15 (9,62%) were examined 6-12 months before the development of AF, 35(22,44%) – 1-2 years before, and all remaining patients have developed AF 2-4 years after the first examination. No significant differences in gender, frequency of essential hypertension, diabetes mellitus, chronic bronchitis, coronary heart disease (CHD) clinical forms have been found.

The results of clinical examination and laboratory tests in patients of I and II groups are present in Table 1. This table demonstrates that the patients of the II group were older and had significant increase of body mass index (BMI), waist circumference, triglycerids and low density lipids (LDL) cholesterol levels comparing with the I group, at the same time there was no significant difference in other characteristics between two groups. Hemodynamics condition, characteristics of signal-averaged ECG, AFDRI in the II group patients after prospective study are demonstrated in Table 2. It is possible to notice that the II group patients had significant increase of laFDV, LVMI, FiP, D_5, Pd and significant decrease of FiP/Pd, E/A, RMS-20 values and AFDRI comparing with the I group, at the same time there was no significant difference between other compared characteristics. 386 (30,36%) and 94 (60,26%) patients of I and II groups respectively had ALP (p<0,05, sensibility, specificity and prognostic significance were 60%, 95% and 19%, respectively), 254 (19,99%) and 105 (67,31%) had pathological values of Pd (p<0,05, sensibility, specificity and prognostic significance were 67%, 96% and 29%, respectively), 273(21,48%) and 118(75,64%) patients of I and II groups had atrial dilation(p<0,05, sensibility, specificity and prognostic significance were 76%, 97% and 30%, respectively). Estimation of the changes of these characteristics after dynamic observation revealed that the patients of the II group starting from the third year and during subsequent observation had significant increase of laFDV, LVMI, FiP, D5, Pd and significant reduction of FiP/Pd, E/A, RMS-20 in comparison both with the results of ob-

Table 1. **Clinical examination and laboratory tests results in the patients of I and II groups (M±m)**

Groups	I group n = 1271	II group n = 156
Characteristics	M±m	M±m
Body mass index (BMI), kg/m^2	29,4±0,2	33,9±0,5*
Waist circumference, cm	101,2±5,1	125,2±1,5*
Age, years	53,7±3,2	65,9±0,5*
Blood glucose, mmol/L	6,4±0,2	6,8±0,5
Total cholesterol, mmol/L	6,3±0,2	6,9±0,3
LDL cholesterol, mmol/L	3,2±0,2	4,3±0,5*
HDL cholesterol, mmol/L	0,8±0,2	0,9±0,2
Triglycerids, mmol/L	2,1±0,2	3,6±0,5*

Comment: * significant difference comparing with the I group (p<0,05).

Table 2. **Hemodynamics condition, signal-averaged ECG characteristics, AFDRI in patients of II groups after dynamic observation in prospective study (M±m and 95% CI of mean values[1])**

Groups of patients	I group[2] n = 1271	II group n = 156 Observation before AF development (years)				
Characteristics		4-4,5 years[2]	3 years[2]	2 years[2]	1 year[2]	>0.5 years[2]
LVEF, %	58,43±0,23 49-71	57,83±0,76 48-69	56,84±0,77 47-66	56,64±0,76 47-68	57,89±0,85 48-69	58,87±0,97 49-71
E/A, relative units	1,14±0,02 0,96-1,32	1,01±0,02[3] 0,72-1,29	0,95±0,02[3, 4] 0,71-1,23	0,91±0,02[3, 4] 0,66-1,15	0,86±0,02[3, 4] 0,61-1,11	0,85±0,02[3, 4] 0,61-1,09
laFDV, mL/m^2	25,37±0,44 18-33	30,06±0,52[3] 24-38	31,56±0,53[3, 4] 25-39	32,96±0,51[3, 4] 25-41	34,79±0,64[3, 4] 28-43	35,93±0,52[3, 4] 29-45
LVMI, g/m^2	128±0,3 115-143	132±0,3[3] 122-143	134±0,3[3, 4] 123-145	135±0,3[3, 4] 127-148	136±0,3[3, 4] 128-150	138±0,3[3, 4] 128-152
FiP-P, ms	116±0.5 93-134	138±1[3] 125-151	141±1[3, 4] 126-154	142±1[3, 4] 129-155	143±1[3, 4] 130-155	144±1[3, 4] 132-155
D5, ms	25±0,1 10-30	26±0,5[3] 20-32	27±0,4[3, 4] 23-33	31±0,5[3, 4] 26-36	34±0,3[3, 4] 30-38	37±0,3[3, 4] 33-41
RMS-20, μV	4,2±0,04 2,3-5,2	3,3±0,07[3] 2,2-4,3	2,9±0,07[3, 4] 2,0-3,7	2,7±0,07[3, 4] 1,7-3,5	2,6±0,07[3, 4] 1,6-3,3	2,4±0,07[3, 4] 1,4-3,2
Pd, ms	31±1 17-52	42±1[3] 35-59	52±1[3, 4] 39-63	57±1[3, 4] 51-65	65±1[3, 4] 58-78	67±0,6[3, 4] 59-79
FiP-P/Pd, relative units	3,74±0,05 5,39-2,41	3,29±0,03[3] 3,67-2,53	2,71±0,01[3, 4] 3,23-2,34	2,49±0,02[3, 4] 2,59-2,31	2,20±0,02[3, 4] 2,51-2,02	2,15±0,02[3, 4] 2,33-2,01
AFDRI, relative units	24,18±2,34 2,31-54,17	10,25±1,8[3] 1,93-28,57	8,57±1,15[3] 1,28-19,44	0,43±0,09[3, 4] 0,12-1,34	0,29±0,04[3, 4] 0,05-0,7	0,12±0,02[3, 4] 0,01-0,5

Comment:
[1] M±m is above mean values, 95% CI is below mean values, [2] average results during observation period, [3] significant difference of characteristics in comparison with the I group, [4] significant difference in comparison with the results 4-4,5 years before AF development (p<0,05).

servation that had been done 4-4,5 years before and the results of the I group, at the same time no significant difference between other characteristics has been found. Starting from the second year of observation and during follow-up observation patients of the II group had significant reduction of AFDRI (95% and more, in average) comparing both with the precedent results of 3 years before and with the I group (Table 2). AF development correlated (r>0,7 was considered significant) with age above 60 years, BMI>30 kg/m^2, RMS-20<3,1 μV, E/A<0,95, laFDV > 30mL/m^2, Pd > 55ms, FiP > 135 ms, FiP/Pd < 2,5 relative units, AFDRI values less than 0,5 relative units, detection of 1200 and more AE per 24 hours (Table 3). Detection of FiP/Pd ⩽2,5 relative units, together with FiP ⩾ 135 ms and/or laFDV > 30mL/m^2 together with AFDRI reduction by 35% and more during each 3-4 months of observation comparing with initial levels correlated with AF development during 1-2 years (r=0,93, OR=16,2, CI=14,7-17,9), and if AFDRI value was ⩽ 0,5 and its subsequent reduction by 70% and more during 1-3 months of observation correlated with AF development during 6 months after observation (r = 0,95, OR= 17,6, CI = 16,7-18,4).

Nowadays it is known that all cardiovascular diseases including MS can cause progressing structural atrial and ventricular remodeling that leads to electric dissociation, shortening of refractory period and local discontinuity of conduction in atrial myocardium, that in its turn can provoke multiple re-entry waves and AF development [1, 2, 3, 4]. It is worth to notice that the presence of frequent AE and/or short asymptomatic AF episodes increase the risk of stroke and other complications [1, 2, 3, 4]. So prediction of AF development and early primary prevention is an important problem of modern cardiology.

1427 patients of age between 45 and 75 years with MS and AE underwent prospective study. After inclusion each patient had been observed during the period from 1 to 4-5 years, presence or absence of AF development during this period was considered the endpoint of this study. 10,93% of observed patients

Table 3. **Correlation (r > 0,7) and OR of clinical observation and instrumental tests results of AF development in patients with MS**

Characteristics	R	OR	OR CI
Age older than 60 years	0,72	2,8	2,0 - 3,5
BMI > 30 kg/m^2	0,83	3,4	2,4 – 3,9
RMS-20 < 3,1 μV	0,75	6,3	5,6 – 6,8
E/A < 0,95	0,77	3,3	2,6 – 3,8
laFDV > 30 mL/m^2	0,79	6,2	5,1 – 6,8
Pd > 55 ms	0,87	8,4	7,9 – 8,9
FiP > 135 ms	0,91	7,6	6,8 – 8,1
FiP/Pd < 2,5 relative units	0,90	11,3	10,4 – 11,9
AFDRI < 0,5 relative units	0,93	14,8	12,3 – 15,8
⩾ 1200AE during 24h of observation	0,86	6,5	5,6 – 7,1

have developed paroxysmal form of AF during 4-4,5 years of prospective observation.

One of the most frequent causes of this arrhythmia is MS that manifests as abdominal obesity, arterial hypertension, hyperglycemia and/or hyperlipidemia that leads to development of left ventricle dysfunction in the majority of cases, left atrium dilation, transmitral flow parameters worsening, etc [1, 2, 3, 4].

More than that, there are predictors like ALP, pathological Pd values that identify delayed, fragmented conduction of excitation that create anatomic background for development of re-entry loop [6], and the frequency of their detection in patients with MS stays in the range of 10-40% [3 ,4, 6, 8, 9, 10]. Similar results have been obtained in the current study. It is worth to mention that according with Framingham study [11] 10-year risk of AF development in this patients was 25-30% (or 12-15% during 4-5 years). Significantly less frequent development of AF in patients with MS in the current study, possibly, was related to exclusion from this study patients with LVEF < 45%, left ventricle aneurism, valvular defects, chronic heart failure III-IV NYHA class.

Results of this study demonstrated that Af development in patients with MS was registered significantly more frequently at the age above 60 years, in case of BMI ⩾ 30 kg/m^2, elevated blood levels of triglycerides, LDL cholesterol, left atrium hypertrophy, presence of ALP and pathological Pd values. Our results are consistent with the results of other studies [1, 2, 3, 4, 6, 9, 10].

Overdistension of atrial myocardium due to their dilation causes progressing sclerosis of cardiac muscle and electric dissociation between muscle bundles and it leads to irregular shortening of refractoriness, development of inhomogeneous conduction in atria that facilitates development and persistence of AF. Presence of dispersion of conduction that can be detected with signal-averaged ECG and Pd demonstrates potentially possible development of reentrant excitation (re-entry) in atrial myocardium or around anatomic block, for example, during the wave movement around pulmonary veins. It is worse to mention that, although detected ALP , Pd pathological values and atrial dilation have enough high sensitivity and specificity, their prognostic knowledge in AF prediction was not higher than 30%. These results have been obtained in previous studies[3, 4, 6]

Nowadays it's known that AE development can be caused by several mechanisms, for example, the presence of trigger activity (early or delayed postdepolarization), re-entry and some other cellular mechanisms [3, 4]. According with the results of invasive electrophysiological studies, it is not possible to see the difference between trigger mechanisms of ventricular extrasystoles development from re-entry and formation of pathological arrhythmogenic focus [3, 4]

Clinical and experimental assays that have been done previously demonstrated that detection of PEIcor LD ⩽ 10 ms indirectly prove re-entry mechanisms and the presence of pathological ectopic focus, and high variability of this characteristic can indicate trigger mechanisms [8].

In this study we estimated AE character using the ratio of PEIcor LD and the number of extrasystoles used for this study, expressed as number of extrasystoles per hour, and we also used characteristics of signal-averaged ECG, for example Fip-P and Pd, that was reflected in AFRDI determination [7]. Reduction of PEIcor LD, AE together with detection of frequent extrasystoles indirectly indicate the presence of pathological ectopic focus and/or development of reentrant excitation (re-entry) in atrial myocardium, that is reflected in AFRDI values reduction [7].

It is worth to notice that the wide variability of AFRDI values (0,01-54 relative units) detected in this study indirectly indicates the presence of AE with different development mechanisms. At the same time patients demonstrated progressing reduction of AFRDI values (averagely by 35% and more during each 3-4 months of examination) 2 years before they developed AF, that can be possibly explained by formation of pathological ectopic focus and/or development of reentrant excitation (re-entry) in atrial myocardium, and also by formation of organic substrate for this arrhythmia development. It can be proved with the results of this study: during this period we registered increase FiP ⩾ 135 ms together with FiP/Pd ⩽ 2,5 relative units, and laFDV ⩾ 30mL/m^2. From the other side, refractory AE probably can provoke the development of irregular conduction of excitation in atria, contributing in development and persistence of AF, that goes along with the results of current study: detection of ⩾ 1200 AE per 24h of observation has strong correlation with the development of this arrhythmia (r=0,86, OR = 8,5, OR CI =7,8-9,1). After formation of another front of AE excitation wave, for example, in case of ectopic focus or re-entry, this wave can undergo fractionation and decay into daughter waves, each one of them can become independent, and the critical amount of travelling waves necessary for AF development can be formed after division of a bigger wave

in some focus with blocked conduction or in case of active movement in the direction of the other atrium [3,4]. It is worth to notice that it is possible to detect local arrhythmic sites in the majority of patients with paroxysmal AF, and at the same time in patients with persistent AF the sites of increased electric activity are disseminated in all atrial myocardium. [2]. Thus it is possible to propose that detection of AE in patients with persistent AF with different mechanisms of its formation is possible to be an independent predictor of this arrhythmia's relapse development.

These results allow to propose that detection of atrial dilation and/or pathological characteristics of signal-averaged ECG, Pd, AE in patients with MS after single examination can determine long-term risk of possible AF development, for example, during 5-10 years and more, but it doesn't mean that this pathology will manifest in the end. The use of long-term risk category is explained by several reasons. At first, around 90% of patients with MS and potential risk of AF development can be placed into the groups of "low" and "moderate" risk, according with known data. At second, according with the opinion of several authors, correction of potentially modifiable factors like body weight, arterial hypertension, blood glucose and lipids levels normalization that facilitate reverse remodeling of atrial myocardium is recommended for the prevention of AF development in patients with MS [3, 4, 6, 10]. That means that all patients with MS at first instance should actively use correction of modifiable factors for primary AF prevention that in the end will lead to the reduction of number of patients with so-called "high" risk of AF development [12].

According with known results, short-term risk reflecting distinct period during which patients with MS are the most likely to develop AF can be determined only if patients undergo dynamic observation not less frequently than once per 3-4 months. It was proved with the results of our study: FiP/Pd ⩽2,5 relative units detection together with FiP ⩾ 135 ms, and/or laFDV > 30 mL/m2 and together with AFDRI reduction by 35% and more during each 3-4 months of observation comparing with the initial results correlated with af development during 1-2 years (r=0,93, OR=16,2, CI=14,7-17,9), and if AFDRI was ⩽ 0,5 relative units, consequent reduction of this characteristic by 70% and more during 1-3 months of observation correlated with af development during 6 months after observation (r=0,95, OR=17,6, CI=16,7-18,4). It is possible that antiarrhythmic drugs should be prescribed in this category of patients for AF primary prevention apart of modifiable risk factors correction, starting from II class of antiarrhythmics and if these drugs aren't effective medicines of III(I) classes or other treatment methods should be used [12].

Conclusions

1. Patients older than 60 years with MS and BMI⩾30kg/m2, elevated levels of triglycerides, LDL cholesterol are put into the risk group of AF development.

2. Detection of atrial dilation, AE and pathological Pd values of signal-averaged ECG in patients with MS characterize the presence of long-term risk of Af development, for example, in 5-10 years, but it does not imply that this pathology will appear in the end.

3. Short-term risk of AF development in patients with MS reflecting the terms of possible development of this arrhythmia is estimated according with AFDRI not less frequently than once per 3-4 months.

4. Reduction of AFDRI values by 35% and more in patients with MS during each 3-4 months of observation comparing with initial values determines the risk (if OR>16) of AF development during 1-2 years, and if detected AFDRI⩽0,5 relative units with subsequent reduction by 70% and more each 1-3 months it determines the risk (if OR>17) of AF development during 6 months after observation.

Conflict of interest: None declared

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