Kardiologia Polska 2016; 74, 8: 754–761; DOI: 10.5603/KP.a2016.0039 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Links between parameters of long-term latent memory and progression from paroxysmal to permanent atrial fibrillation during a five-year observation period. A preliminary study

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Abstract

Background and aim: As cognitive function is the most vulnerable human feature, its impairment may precede the occurrence of symptoms of cardiovascular system disorders, e.g. atrial fibrillation (AF). In this way, cognitive impairment may not only be a complication of AF, but also a marker of its progression. This study aims to test this hypothesis.

Methods: Of 35 patients with AF, 23 (66%) had paroxysmal and 12 (34%) had permanent arrhythmia at the start of the study. At both the start of the study and after 5.86 ± 3.7–7.05 years of follow-up, the following neuropsychological tests were performed using the Beck Depression Inventory, Parts A and B of the Trail Making Test, eight trials from the Rey Auditory Verbal Learning Test (RAVLT), and the Stroop test.

Results: Patients who maintained paroxysmal AF for the whole study observation period (n = 10) had a significantly greater score in the sixth (A6) and seventh (A7) RAVLT trials (pertaining to parameters of long-term latent memory) at the start of the study. An association between lower RAVLT A6 and A7 trial scores and the risk of paroxysmal arrhythmia progression to permanent AF was confirmed using the Cox proportional hazards regression model and Kaplan-Meier survival analysis.

Conclusions: A better long-term latent memory RAVLT score was associated with a favourable prognosis of sinus rhythm maintenance. Cognitive impairment should be investigated in patients with AF for the purpose of evaluating the patient's prognosis, subclinical injury to the cardiovascular system, and the ability to comply with treatment.

Key words: atrial fibrillation, cognitive impairment, latent memory, risk factors

Kardiol Pol 2016; 74, 8: 754–761

INTRODUCTION

Atrial fibrillation (AF) is the most common form of chronic cardiac arrhythmia. It is associated with greater risk of both cardiological and non-cardiological complications, including a decrease in health-related quality of life, cardiac failure, stroke, and death [1, 2]. This type of arrhythmia is also related to cognitive impairment [3–8]. This form of mental disorder may appear in patients both with organic lesions on neuroradiological brain examination (indicative of, for example, ischaemic stroke, silent cerebral ischaemia, silent brain infarct, damage in the blood vessels of the brain, white matter lesions, or loss of cortical, subcortical, or hippocampal volume) and without [6, 9–12]. The following pathomechanisms of the relationships between AF and cognitive impairment have been suggested: (a) stroke due to embolus of a cerebral artery; (b) asymptomatic cerebral artery microembolism with mate-

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Received: 02.11.2015 **Accepted:** 11.02.2016 **Available as AoP:** 01.04.2016

rial of cardiac origin, e.g. due to insufficient anticoagulation; (c) haemodynamic complications of atrial arrhythmia leading to a decrease in cerebral blood flow; (d) anticoagulation complications with haemorrhagic stroke; (e) systolic or diastolic cardiac failure; and (f) the effect of characteristics and comorbidities leading to heart and vascular injury, such as: increased age, gender, hypertension, diabetes mellitus, hyperlipidaemia, obesity, low physical activity, and systemic inflammatory status [10, 13–18]. Relationships between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and left atrium dilatation are also reported [19–21]. The evaluation of cognitive function in every patient with AF is, therefore, indicated due to these complicated relationships, mainly for the purpose of diagnosing subclinical vascular injury and determining the patient's ability to comply with physician recommendations [22].

On the other hand, the cognitive functions are one of the most sensitive attributes of the brain. For this reason, they are, in addition, vulnerable to clinically latent vascular injury that is secondary to the arrhythmia complications and comorbidities recognised as risk factors for atherosclerosis and AF [13–15]. In this way, cognitive impairment may precede clinically overt symptoms of vascular injury, both in the brain and in the extracerebral vascular beds, e.g. sub form of coronary or peripheral artery disease, as well as AF and cardiac failure. This suggests consideration of cognitive impairment as a predictive factor for the symptomatic disclosure of cardiovascular disorders. On the other hand, cognitive impairment may result in a lack of compliance with therapeutic recommendations, which may favour the development of arrhythmia substrate and bleeding complications due to anticoagulant misuse [23, 24]. Both of these clinical conditions can lead to progression in arrhythmia and, in a vicious circle mechanism, to the aggravation of cognitive impairment. On the basis of the aforementioned premises, we hypothesised that cognitive impairment might be a marker of subclinical vascular injury in extracerebral vascular beds. To verify this hypothesis, we examined the relationships between neuro-cognitive test scores at the beginning of a patient's observation and the type of AF (paroxysmal or permanent) after an average of five years of observation, in an attempt to identify cognitive impairment severity as a marker for further cardiac arrhythmia progression.

METHODS

Study group

Eighty-five patients with AF were studied. The inclusion criteria were as follows: (a) paroxysmal, persistent, or permanent AF; (b) the ability to perform a six-minute walk test (6MWT); (c) aged 30–70 years; and (d) written consent for study participation. Exclusion criteria were as follows: (a) a history of irregular medication and (b) a history of stroke or documented dementia.

All the patients were initially hospitalised due to AF. They were classified as having paroxysmal or persistent and permanent arrhythmia. All the patients underwent blood sampling for biochemical examination, including blood morphology, glucose, lipids, creatinine, international normalised ratio (INR), thyroid-stimulating hormone (TSH), B-type natriuretic peptide (BNP), and C-reactive protein (CRP). An electrocardiogram (ECG), 6MWT, and echocardiography were also performed for every patient. After nearly six years of observation, the following criteria for the distribution of patients were admitted: permanent AF was defined as arrhythmia, which (based on the available documentation) did not give up cardioversion or, in the opinion of the treating physician, did not promise a longer maintenance of sinus rhythm or rhythm control strategy was, in his opinion, more risky than a rate control strategy. This arrhythmia also does not cause palpitations. Paroxysmal was defined as arrhythmia, appearing periodically, subsides spontaneously or after cardioversion, giving symptoms of palpitations and absent during the control visit day (ECG revealed the presence of sinus rhythm). After, on average, 2025.2 ± 314.8 days (median ± range: 5.86 ± 3.7–7.05 years), all the patients were asked to attend a control visit with the same examination as carried out previously. Thirty-five patients attended this control investigation.

Neuropsychological assessment

In neuropsychological assessment, during every visit, several tests were used: Trial Making Test (TMT A and B) to estimate psychomotor speed (Part A), visual-spatial working memory and the ability to switch attention (Part B); Stroop test to examine the original reading speed (Part one), verbal working memory and executive functions (Part two); and Rey Auditory Verbal Learning Test (RAVLT) to assess verbal memory, performance auditory declarative memory (both direct and deferred), and verbal learning efficiency. Depressive symptoms were evaluated by Beck Depression Inventory (BDI). Only the results obtained from two visits were taken for analysis.

Measured outcomes

The type of AF (paroxysmal or permanent) at the end of the study. The results of the cognitive tests used.

Ethics

All the subjects gave their informed consent to participate in this study, which was approved by the Local Ethics Committee. The investigation was conducted in compliance with the Declaration of Helsinki for medical research.

Statistical analysis

Statistical analysis was conducted using a licensed version of StatSoft, Inc. (2011) STATISTICA (a data analysis software system) version 10. The normal distribution of the study variables was checked using the Shapiro-Wilk test. The results were mainly presented as the mean ± standard deviation (SD) or 'n' and percentage. The statistical significance of the

Table 1. Comparison of demographic and clinical data of patients with paroxysmal atrial fibrillation (AF) at the beginning of the study (n = 23) based on arrhythmia type after the follow-up period

Parameter	Paroxysmal AF at the end of the study (n = 10)	Permanent AF at the end of the study (n = 13)	P
Age [years]	64.0 ± 4.1	68.0 ± 9.3	0.22
Male gender	7 (70%)	6 (47%)	0.25
Diabetes mellitus	2 (20%)	2 (15%)	0.78
Hypertension	8 (80%)	9 (69%)	0.58
Coronary artery disease	3 (30%)	3 (23%)	0.72
CHA_2DS_2-VASc [score]	3.2 ± 1.9	3.2 ± 1.5	0.88
HAS-BLED [score]	2.1 ± 0.9	1.9 ± 0.9	0.67
Body mass index [kg/m^2]	30.9 ± 2.0	29.5 ± 2.1	0.39
Left ventricle size [mm]	49.5 ± 5.4	48.6 ± 4.9	0.70
Left atrium size [mm]	46.9 ± 5.5	44.6 ± 3.9	0.30
Interventricular septum thickness [mm]	12.0 ± 1.9	11.3 ± 1.7	0.39
Ejection fraction [%]	55.6 ± 14.5	59.7 ± 7.4	0.40
B-type natriuretic peptide [pg/mL]	350.5 ± 374.6	342.3 ± 401	0.96
TSH [mU/L]	1.2 ± 0.3	1.2 ± 0.6	0.78
Creatinine [mg/dL]	1.1 ± 0.2	1.2 ± 0.4	0.59
C-reactive protein	4.9 ± 5.3	2.3 ± 1.4	0.26
Total cholesterol [mg/dL]	181.1 ± 48.6	201.8 ± 56.2	0.41
HDL cholesterol [mg/dL]	52.4 ± 16.3	42.8 ± 14.4	0.21
LDL cholesterol [mg/dL]	121.7 ± 34.0	120.9 ± 30.4	0.96
Triglycerides [mg/dL]	156.5 ± 77.0	216.6 ± 175.6	0.38
Blood glucose [mg/dL]	119.8 ± 54.1	98.2 ± 23.2	0.22
Haemoglobin [g/dL]	14.6 ± 2.1	14.7 ± 1.4	0.85
Haematocrit [%]	42.7 ± 6.1	43.0 ± 3.4	0.89
BDI score	12.6 ± 3.9	16.8 ± 9.9	0.27
TMT-A score	43.5 ± 7.3	67.1 ± 45.4	0.17
TMT-B score	87.5 ± 20.6	145.2 ± 88.1	0.09
RAVLT-A1 score	4.8 ± 1.3	4.6 ± 1.1	0.72
RAVLT-A2 score	8.3 ± 2.1	7.0 ± 1.3	0.12
RAVLT-A3 score	9.6 ± 2.1	8.8 ± 2.0	0.41
RAVLT-A4 score	11.4 ± 1.3	10.1 ± 1.6	0.078
RAVLT-A5 score	12.1 ± 1.1	11.3 ± 2.1	0.49
RAVLT-B1 score	4.6 ± 1.2	4.6 ± 1.4	0.99
RAVLT-A6 score	10.0 ± 2.0	7.3 ± 2.2	0.01
RAVLT-A7 score	10.4 ± 1.6	8.1 ± 2.9	0.01
Stroop test 1 score	29.4 ± 6.2	34.1 ± 10.3	0.27
Stroop test 2 score	88.5 ± 21.7	100.0 ± 26.5	0.33
6MWT [m]	277.5 ± 58.3	248.1 ± 78.0	0.33

Data are presented as mean ± standard deviation; TSH — thyroid-stimulating hormone; HDL — high-density lipoprotein; LDL — low-density lipoprotein; BDI — Beck Depression Inventory; TMT-A — Trail Making Test Part A; TMT-B — Trail Making Test Part B; RAVLT — Rey Auditory Verbal Learning Test; RAVLT A1–A7 — trials involved in the RAVLT test; 6MWT — six-minute walk test

differences between patients with paroxysmal and permanent cardiac arrhythmia was verified using the unpaired Student's t-test and Fisher's exact test. The two-factorial ANOVA method with repetitions and the least significant difference post-hoc test were used to compare the differences in outcomes for the cognitive tests used between patients with the two arrhythmia

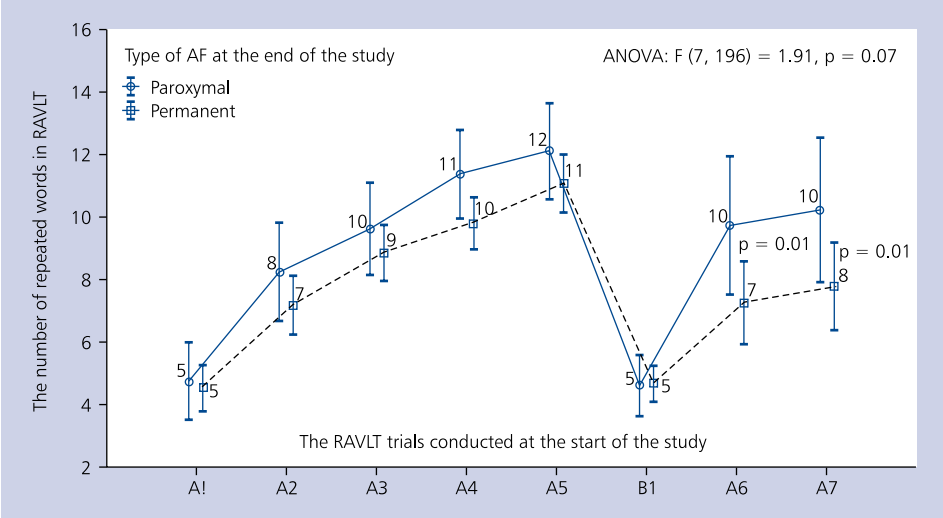

Figure 1. Values for the Rey Auditory Verbal Learning Test (RAVLT) at the beginning of the study in relation to the type of atrial fibrillation (AF) experienced at the end of the investigation

types and clinical factors. Logistic regression was applied to check the relationships between the type of AF at the end of the study and the RAVLT A7 trial outcome. Adding the other variables into the logistic regression model made it statistically not significant. Survival analysis was conducted for the 35 subjects, using Kaplan-Meier's method with Cox's F test for two groups and the Cox proportional hazards model. A receiver operating characteristic (ROC) curve, created by plotting the true positive rate against the false positive rate for various threshold settings, was drawn to determine the best RAVLT test value for predicting the maintenance of paroxysmal AF.

RESULTS

Thirty-five patients with AF were included in the analysis. At the start of the study, 23 (66%) had paroxysmal or persistent arrhythmia and 12 (34%) had permanent AF. After an observation period lasting, on average, more than five years, only 10 of the 23 (43%) patients still had sinus rhythm and paroxysmal type of AF, but in 13 (57%) patients this atrial arrhythmia had become permanent. Patients with paroxysmal AF, both at the beginning and at the end of the study, did not differ in relation to demographic, clinical, or biochemical (including BNP, CRP, TSH, creatinine, INR, blood lipid, and glucose concentration) values or echocardiographic parameters (e.g. left atrium size, ejection fraction, features of diastolic left ventricular failure, and valve function) in comparison with patients in whom a change in arrhythmia type was observed (Table 1). However, patients who had paroxysmal AF throughout the whole study observation period had significantly greater scores in the sixth (A6) and seventh (A7) RAVLT trials and a borderline effect of AF type on the RAVLT scores as a whole at the start of the study (Fig. 1). The association between lower RAVLT A6 and A7 trial scores (parameters of long-term latent memory) and

Table 2. Logistic regression method for determining the effect of the RAVLT A7 trial on change of arrhythmia type among patients initially diagnosed with paroxysmal atrial fibrillation (χ^2 = 4.11; p = 0.043)

Parameter	Constant variable	RAVLT A7 score
Estimation	–4.18	0.34
Standard error	2.04	0.20
t(28)	–2.05	1.69
P	0.05	0.10
–95% CI	–8.35	–0.07
+95% CI	0.0008	0.76
Chi² Wald statistic	4.19	2.85
P	0.041	0.09
Odds ratio for unit	0.015	1.41
–95% CI	0.0002	0.93
+95% CI	1.001	2.14

CI — confidence interval

the risk of paroxysmal arrhythmia progression into permanent AF was confirmed by logistic regression (only the model with a A7 trial score was statistically significant) (Table 2), Cox proportional hazards regression (Table 3), and Kaplan-Meier survival analysis, whereby a median value of 10 was established as the discriminative value for RAVLT A7 (Fig. 2). However, in the analysis using an ROC curve, the cut-off value for both the RAVLT A6 and A7 trials was determined as being a score of 11 (Fig. 3). Analysis of the RAVLT A7 trial revealed the following values for the diagnosis of paroxysmal AF after an observation lasting an average of five years: sensitivity — 50%,

Table 3. Cox proportional hazards regression model for the duration of paroxysmal atrial fibrillation (χ^2 = 26.7168; p = 0.031)

Parameters	Beta	Standard error	t	Wald statistics	P	Relative hazard ± 95% CI
Age	0.016	0.047	0.35	0.12	0.73	1.0 ± 0.9–1.1
Gender	0.11	0.74	0.14	0.02	0.89	1.1 ± 0.2–4.7
Diabetes mellitus	0.42	1.03	0.41	0.17	0.68	1.53 ± 0.2–1.4
Hypertension	1.17	0.89	1.32	1.73	0.19	3.2± 0.5–18.5
TSH	–0.75	0.89	–0.83	0.70	0.40	0.5 ± 0.1–2.7
Creatinine	–2.79	1.42	–1.96	3.84	0.052	0.06 ± 0.004–1.0
LDL-C	–0.02	0.019	–0.88	0.77	0.38	0.98 ± 0.95–1.02
Glucose	–0.03	0.012	–2.08	4.32	0.038	0.97 ± 0.95–0.99
Triglycerides	0.005	0.003	1.61	2.58	0.11	1.01 ± 0.99–1.1
BDI	–0.03	0.040	–0.65	0.43	0.51	0.97 ± 0.9–1.05
TMT-B	–0.0001	0.009	–0.01	0.001	0.99	0.99 ± 0.98–1.0
BNP	0.002	0.002	1.12	1.25	0.26	1.0 ± 0.99–1.01
Stroop 2 test	–0.05	0.021	–2.26	5.13	0.024	0.95 ± 0.92–0.99
6MWT	–0.003	0.005	–0.62	0.39	0.53	0.99 ± 0.99–1.01
RAVLT A7	–0.62	0.18	–3.52	12.4	0.0004	0.53 ± 0.38–0.76

TSH — thyroid-stimulating hormone; LDL-C — low-density lipoprotein cholesterol; BDI — Beck Depression Inventory; TMT-B — Trail Making Test Part B; BNP — B-type natriuretic peptide; 6MWT — six-minute walk test; RAVLT — Rey Auditory Verbal Learning Test; RAVLT A7 — trial contained in the RAVLT test

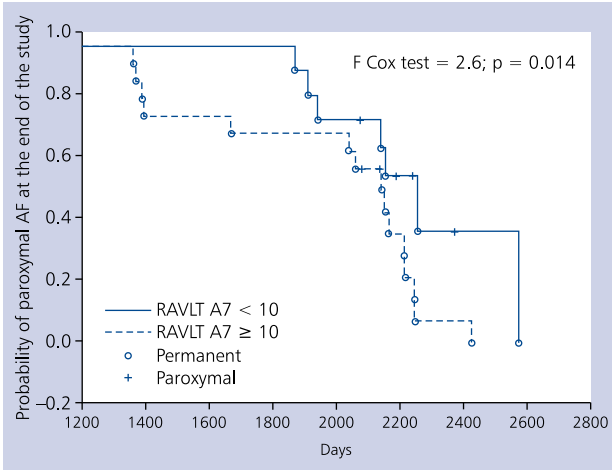

Figure 2. Kaplan-Meier curve showing maintenance of paroxysmal arrhythmia in relation to the median value of the outcome of the seventh trial of the Rey Auditory Verbal Learning Test (RAVLT); AF — atrial fibrillation

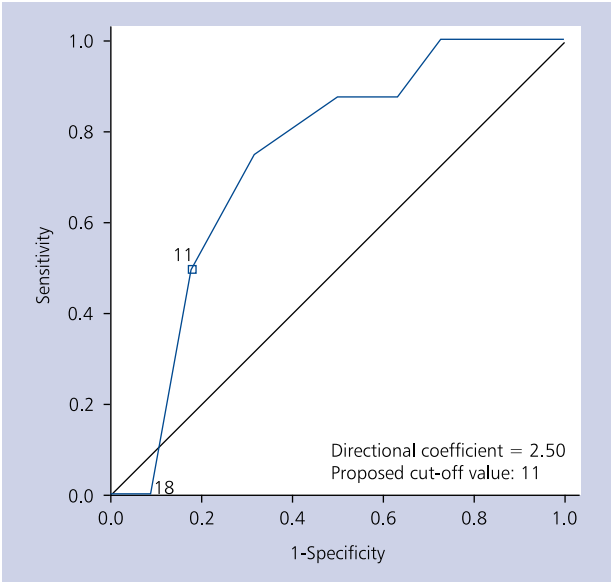

Figure 3. Receiver operating characteristic curve for the value of the seventh Rey Auditory Verbal Learning Test (RAVLT) trial in predicting the maintenance of paroxysmal atrial fibrillation

specificity — 83%, positive predictive value — 55%, and negative predictive value — 79%. One hundred per cent sensitivity for paroxysmal AF maintenance was obtained when the cut-off value for the RAVLT A7 trial was a score of 7, and 100% specificity when the RAVLT A7 score was 13 (Fig. 3). However, the Kaplan-Meier curve for such values did not achieve statistical significance (p = 0.079), in spite of a value of 10, as presented in Figure 2. The results of remaining used tests did not reveal a similar predictive value.

DISCUSSION

We found that only 43% of the patients with paroxysmal AF in this study maintained this type of arrhythmia over an average five-year observation period. A better functioning long-term latent memory, expressed as an RAVLT A6 and A7 trial score greater than 10, was the only statistically significant variable

that distinguished patients who maintained their initial AF type from those who developed permanent AF (Table 1). This observation was confirmed in a significant model of logistic regression, but without confirmation of RAVLT A7 importance as a significant, independent risk factor (Table 2); in two-factorial ANOVA with eight repetitions (Fig. 1); in Kaplan-Meier analysis of two groups (Fig. 2); and in multifactorial analysis with the Cox proportional hazards regression model (Table 3). The last of the analyses highlighted that greater RAVLT A7 and Stroop test scores were significant independent predictors for the length of time an efficient rhythm control strategy could be maintained. This effect was not observed for known atherosclerosis and atrial arrhythmia risk factors, such as hypertension, diabetes mellitus, CHA_2DS_2-VASc and HAS-BLED scores, BNP blood concentration, ejection fraction, and left atrium diameter, which failed to achieve a statistically significant effect in the Cox proportional hazards regression model for survival analysis (Table 3). This suggests that cognitive impairment, especially the sub form of dysfunction in long-term latent memory revealed by the RAVLT A6 and A7 trials and reading ability examined using the Stroop test, had greater sensitivity for detecting subclinical vessel injury and an unfavourable arrhythmia course than well-documented clinical, biochemical, and echocardiographic factors.

To the best of our knowledge, this is the first report to consider stronger forms of cognitive impairment, especially concerning long-term latent memory, as a predictor of rhythm control strategy failure in patients with paroxysmal AF. Previous papers showed cognitive impairment as a complication of cardiac arrhythmia, not as an early marker of more advanced cardiovascular dysfunctions predisposing patients to AF progression [3–5, 7, 10, 22, 25]. Their authors also suggested that different clinical conditions, e.g. diabetes mellitus or hypertension, may predispose patients to impairments in various mental abilities (or cognitive domains), such as attention, memory, early (working) memory, latent memory, judgment, evaluation, reasoning, problem solving, decision making, and comprehension, which are related to the correct functioning of the frontal cortex or hippocampus. The results of our study point to the strategy of rhythm control as being more effective in patients with paroxysmal AF and greater RAVLT A6 and A7 and Stroop test scores (Table 3). Greater RAVLT A6 and A7 scores revealed better long-term latent memory function, and higher scores in the Stroop test are associated with better cognitive flexibility, resistance to interference from outside stimuli, creativity, psychopathology, and cognitive complexity.

The results obtained may be explained either by greater severity of AF course in the participants at the beginning of the study, which result in both arrhythmia progression (due to electrical and mechanical left atrium remodelling) and greater cognitive impairment, or by the presence in some study participants of a stronger effect of arrhythmia and comorbidities on vascular injury, which resulted in greater cognitive impairment at the start of the study and earlier progression from paroxysmal to permanent AF. This may be recognised as a practical contribution of our study. Cognitive impairment and silent brain injury may also be suggested as a guide for prescribing anticoagulation treatment for patients at low risk of AF to prevent cognitive decline [11, 17].

However, as with many authors, we could not avoid some methodological shortcomings in our study, which may affect the interpretation of our findings. The most important was the small number of study participants, which reduces the reliability our results, the survival analysis in particular. On the other hand, the credibility of the analysis was improved by the fact that during both visits the neuropsychological tests were performed by the same psychologists, biochemical determinations were made in the same certified in-hospital laboratory, and ECG and echocardiography were carried out by the same cardiologist.

CONCLUSIONS

1. Better long-term latent memory expressed by greater RAVLT A6 and A7 scores was associated with a favourable prognosis of sinus rhythm maintenance in patients with paroxysmal AF in almost six-year long follow-up.
2. Cognitive impairment should be investigated in patients with AF for the purpose of evaluating the patient's prognosis (defined as conversion to permanent AF), as well as diagnosis of vascular dementia presence, which is important in estimation of potential ability of compliance with treatment, including anticoagulant use.

Conflict of interest: *none declared*

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Cite this article as: Mietła B, Budzyński J, Bieliński M et al. Links between parameters of long-term latent memory and progression from paroxysmal to permanent atrial fibrillation during a five-year observation period. A preliminary study. Kardiol Pol, 74: 754–761. doi: 10.5603/KP.a2016.0039.

Związek parametrów długotrwałej pamięci utajonej z progresją od napadowego do utrwalonego migotania przedsionków w pięcioletniej obserwacji. Badania wstępne

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Streszczenie

Wstęp i cel: Ponieważ funkcjonowanie poznawcze jest jedną z najbardziej wrażliwych cech ludzkich, to jego zaburzenia mogą poprzedzać wystąpienie objawów chorób układu sercowo-naczyniowego, np. migotania przedsionków (AF). W ten sposób upośledzenie funkcji poznawczych może być nie tylko powikłaniem AF, lecz także markerem jego progresji. Celem badania było sprawdzenie tej hipotezy.

Metody: Spośród 35 pacjentów z AF u 23 (66%) chorych na początku badania stwierdzono napadowe AF, a u 12 (34%) osób utrwaloną arytmię. Zarówno na początku badania, jak i po 5,86 ± 3,7–7,05 latach obserwacji dokonano oceny neuropsychologicznej z wykorzystaniem Skali Depresji Becka, części A i B testu łączenia punktów (TMT), ośmiu prób z testu słuchowo-werbalnego uczenia się Reya (RAVLT) oraz testu Stroopa.

Wyniki: Pacjenci, u których utrzymało się napadowe AF w okresie całego badania (n = 10), charakteryzowali się istotnie większym wynikiem w szóstej (A6) i siódmej (A7) próbie RAVLT (odnoszących się do parametrów długoterminowej pamięci utajonej) na początku badania. Związek między niższymi wynikami prób RAVLT A6 i A7 a ryzykiem progresji arytmii z napadowego do utrwalonego AF został potwierdzony przy użyciu modelu proporcjonalnego hazardu Coxa i analizy przeżycia Kaplana-Meiera.

Wnioski: Lepsze wyniki długoterminowej pamięci utajonej wiązały się z korzystnym rokowaniem utrzymania rytmu zatokowego. Zaburzenia poznawcze powinny być badane u pacjentów z AF w celu oceny rokowania chorego, subklinicznej dysfunkcji układu sercowo-naczyniowego, a także zdolności do przestrzegania zaleceń terapeutycznych.

Słowa kluczowe: migotanie przedsionków, upośledzenie funkcji poznawczych, pamięć długotrwała, czynniki ryzyka

Kardiol Pol 2016; 74, 8: 754–761

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Praca wpłynęła: 02.11.2015 r. **Zaakceptowana do druku:** 11.02.2016 r. **Data publikacji AoP:** 01.04.2016 r.