

## Comparison of Cognitive Functions between Paroxysmal and Persistent Atrial Fibrillation Patients without Clinical Stroke

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### Abstract

**Objective:** To compare cognitive functions between paroxysmal and persistent atrial fibrillation patients without clinical stroke, in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains scores.

**Methods:** A comparative study that compared MoCA-Ina scores between paroxysmal and persistent AF patients without clinical stroke, who came for treatment at the Cardiology Clinic Dr. Hasan Sadikin General Hospital, Bandung and Dustira Hospital, Cimahi from September 2018–January 2019.

**Results:** Sixty four subjects were recruited, consisted of 24 paroxysmal and 40 persistent AF patients. There were no difference in clinical characteristics between two groups, except that there were more subjects in the persistent AF group using anticoagulants therapy: 97.5% vs 62.5% ( $p=0.005$ ) and more prevalence of type 2 Diabetes Mellitus in the paroxysmal AF group: 25% vs 2.5% ( $p=0.009$ ). Cognitive impairment (MoCA-Ina score  $<25$ ) were seen in 70.8% of paroxysmal AF group and 82.5% of persistent AF group ( $p=0.274$ ). The mean MoCA-Ina total score in the paroxysmal and persistent AF groups were  $21.04\pm 4.75$  vs  $20.70\pm 4.21$  ( $p=0.989$ ), respectively. The median MoCA-Ina cognitive subdomains scores were similar for the two groups ( $p>0.05$ ).

**Conclusion:** There were no differences in cognitive functions between paroxysmal and persistent AF patients, both in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains scores, although in both groups had cognitive decline.

**Keywords:** Atrial fibrillation, cognitive impairment, MoCA-Ina, paroxysmal AF, persistent AF

pISSN: 2302-1381;  
eISSN: 2338-4506;  
<http://doi.org/10.15850/ijih.v8n1.1974>  
IJHS. 2020;8(1):32-7

Received:  
January 28, 2020

Accepted:  
May 16, 2020

### Introduction

Many studies have reported a significant association between atrial fibrillation (AF) and cognitive impairment and a faster incidence of dementia, both with and without the occurrence of clinical stroke that preceded it.<sup>1,2</sup> The prevalence of mild cognitive impairment (MCI) and dementia in

AF patients was estimated at 40%, higher than patients without AF.<sup>2,3</sup>

The mechanism of cognitive impairment in AF patients is mostly related to the incidence of cardioembolic stroke, but it is well known that without a stroke, AF also can cause cognitive impairment. Although the mechanisms that play a role in this case are not fully understood, several hypotheses have been stated i.e the occurrence of the silent cerebral infarct (SCI), cerebral hypoperfusion, vascular inflammation and processes involving small vessels (small vessel disease/SVD).<sup>3-5</sup>

Paroxysmal and persistent AF are thought to have different pathophysiology of thrombus formation. Some experts argue that the short

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duration of AF in paroxysmal AF patients is associated with smaller and newly formed thrombus so that early recanalization is easier. In the contrary, thrombus in the persistent AF may be larger due to the larger size of the left atrial auriculum. Besides that the thrombus in persistent AF is more organized and stronger so that it tends to respond less to early recanalization. In addition, persistent AF is also associated with a greater number of lesions than paroxysmal AF. Therefore, persistent AF is considered more associated with a higher incidence of SCI and lower cognitive function as compared to paroxysmal AF, even without previous stroke events.<sup>6</sup>

The MoCA-Ina test (Indonesian version of Montreal Cognitive Assessment) is one of the most frequently used and validated test for cognitive impairment screening.<sup>7</sup> This test has a higher sensitivity and specificity in diagnosing mild cognitive disorders compared to the MMSE (Mini Mental State Examination) test because it covers all cognitive domains including executive functions.<sup>8</sup>

This study was aimed to compare cognitive function between paroxysmal and persistent AF patients without a clinical stroke, in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomains score.

## Methods

This was a comparative study of adult patients (age >18 years) with paroxysmal and persistent AF in the cardiology clinic at Hasan Sadikin Hospital Bandung and Dustira Hospital Cimahi. Patients were excluded if they have had one of the following: a history of clinical stroke, diagnosed as Rheumatic Heart Disease (RHD), a history of central nervous system abnormalities (i.e epilepsy, Parkinson's Disease, Multiple Sclerosis, moderate to severe head injury or brain infections), a history of systemic abnormalities (i.e moderate to severe congestive heart failure, chronic kidney disease, routine hemodialysis or HIV-AIDS), using memory enhancer or other psychopharmaceutical drugs and had a severe impaired vision, hearing and motor function that hampered the examination.

Ethical approval from the Health Research Ethics Committee of the Dr. Hasan Sadikin General Hospital Bandung under the ethical clearance No. LB.04.01/A05/EC/273/IX/2018 was gained prior the study. Sampling was conducted consecutively from September 2018 to January 2019. A comprehensive range of sociodemographic and clinical data were

collected through questionnaires. Cognitive function data was obtained through the MoCA-Ina test. The eligible subjects were examined with MoCA-Ina test after signing the informed consent. The MoCA-Ina test was performed by a trained neurology resident. MoCA-Ina total score and MoCA-Ina cognitive subdomains scores were compared between the two AF groups. The research datas are described using tables according to the variables identified during the study. Data was analyzed using SPSS version 24.0 for Windows. The probability value  $p < 0.05$  is considered statistically significant.

## Results

Sixty four subjects were recruited during the study's period, consisted of 24 paroxysmal and 40 persistent AF patients. The comparison of the basic characteristics of the subjects between the two AF groups was shown on Table 1. There were no significant differences in demographic characteristics (age, gender and education level) between the two AF groups, so that both of groups could be considered homogeneous and could be compared. From the clinical characteristics there were also no statistically significant difference, except for the history of taking anticoagulant therapy and the presence of type 2 DM variables, where there were more subjects in the persistent AF group who used anticoagulant therapy i.e. 97.5% vs 62.5% ( $p = 0.005$ ) and more comorbidities of type 2 DM in the paroxysmal AF group of 25% vs 2.5% ( $p = 0.009$ ). Both of these variables may act as confounding variables which can influence further statistical analysis.

The comparison of the results of the MoCA-Ina test of the subjects between the two AF groups was shown on Table 2. Cognitive impairment (MoCA-Ina total score  $< 25$ ) were found in paroxysmal and persistent AF groups (82.50% vs 70.80%,  $p = 0.274$ ). Similarly, the MoCA-Ina total score was decrease in the both AF groups with a mean of  $21.04 \pm 4.75$  vs  $20.70 \pm 4.27$  ( $p = 0.989$ ), respectively for the paroxysmal and persistent AF groups.

MoCA-Ina cognitive subdomain score were low in both groups, especially the executive functioning and memory, but did not show a statistically significant difference. (Table 2). Domains that were mostly disturbed in the paroxysmal AF group were the executive functioning (95.8%), memory (87.5%) and language (79.2%), while in the persistent AF group were memory (95%), executive

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**Table 1 Subject Characteristics**

Variable	Group		p-value
	Paroxysmal AF (n=24)	Persistent AF (n=40)	
Age (years) Mean±SD	61.32±11.45	60.12±9.59	0.655
Gender	8 (33.30%)	16 (40.00%)	0.594
Male	16 (66.70%)	24 (60.00%)	
Female			
Education (years) Median	9.00 6.00–16.00	9.00 6.00–16.00	0.412
Range (min–max)			
Occupation	23 (95.80%)	38 (95.00%)	1.000
Active	1(4.20%)	2 (5.00%)	
Not active			
Duration of AF (years) Median	2.25 0.02–20.00	4.00 0.08–21.00	0.237
Range (min–max)			
Antiarrhythmic therapy	22 (91.70%)	38 (95.00%)	0.627
Yes	2 (8.30%)	2 (5.00%)	
No			
Anticoagulant therapy	12 (50.00%)	38 (95.00%)	0.005*
Warfarin	3 (12.50%)	1 (2.50%)	
NOAC	9 (37.50%)	1 (2.50%)	
None			
INR value	21(87.50%)	24 (60.00%)	0.207
<2	3 (12.50%)	10 (25.00%)	
2–3	0 (0.00%)	6 (15.00%)	
>3	0	6	
Comorbidities			
Hypertension	16 (66.70%)	19 (47.50%)	0.136
Type 2 DM	6 (25.00%)	1 (2.50%)	0.009*
Ischemic Heart Disease	12 (50.00%)	12 (30.00%)	0.110
Heart Failure	12 (50.00%)	28 (70.00%)	0.110
CHA <sub>2</sub> DS <sub>2</sub> -VASc scores			
Median	3.00	3.00	0.068
Range (min–max)	1.00–6.00	0.00–5.00	

Note: \*statistically significant, SD: standard deviation, min: minimal, max: maximal, AF: atrial fibrillation, NOAC: non vitamin K-antagonist oral anticoagulant, INR: International Normalized Ratio, DM: diabetes mellitus, CHA<sub>2</sub>DS<sub>2</sub>-VASc: Congestive heart failure, hypertension, Age ≥75 years, diabetes, stroke, vascular disease, Age ≥65 years, Sex category-female

functioning (90%) and attention (82.5%). Orientation domain was less disturbed in both groups. (Table 2)

### Discussion

In this study, cognitive impairment in AF patients was prominent, as shown by the high proportion of low MoCA-Ina total score and

its cognitive subdomain score. The average MoCA-Ina total score in this study was lower than the average MoCA total score for the normal population with the same age (23.20 ± 3.96).<sup>9</sup> The proportion of cognitive impairment in this study were almost the same with one study in Indonesia, that was 86.70%, with mean MoCA-Ina total score was 21.77±2.87.<sup>10</sup> Deficits in executive functioning and memory

**Table 2 Results of MoCA-Ina Test**

Variable	Group		p-value
	Paroxysmal AF (n=24)	Persistent AF (n=40)	
Cognitive decline based on MoCA-Ina score			0.274
≥25	7 (29.20%)	7 (17.50%)	
<25	17 (70.80%)	33 (82.50%)	
MoCA-Ina total score			
Mean±SD	21.04±4.75	20.70±4.27	0.989
Attention domain			
Median score	4.00	4.00	0.938
Range (min-max)	2.00-6.00	0.00-6.00	
Normal	6 (25.0%)	7 (17.5%)	
Abnormal	18 (75.0%)	33 (82.5%)	0.470
Memory domain			
Median score	2.00	2.00	0.943
Range (min-max)	0.00-5.00	0.00-5.00	
Normal	3 (12.5%)	2 (5.0%)	
Abnormal	21 (87.5%)	38 (95.0%)	0.355
Language domain			
Median score	4.00	4.00	0.842
Range (min-max)	1.00-6.00	2.00-6.00	
Normal	5 (20.8%)	9 (22.5%)	
Abnormal	19 (79.2%)	31 (77.5%)	0.876
Visuospatial domain			
Median score	3.00	3.00	0.825
Range (min-max)	2.00-4.00	2.00-4.00	
Normal	9 (37.5%)	15 (37.5%)	
Abnormal	15 (62.5%)	25 (62.5%)	1.000
Executive functioning domain			
Median score	1.00	1.00	0.611
Range (min-max)	0.00-4.00	0.00-4.00	
Normal	1 (4.2%)	4 (10.0%)	
Abnormal	23 (95.8%)	36 (90.0%)	0.642
Orientation domain			
Median score	6.00	6.00	0.993
Range (min-max)	3.00-6.00	2.00-6.00	
Normal	16(66.7%)	27(67.5%)	
Abnormal	8(33.3%)	13(32.5%)	0.945

Note: SD: Standard Deviation, min: minimal, max: maximal, MoCA-Ina: Indonesian version of *Montreal Cognitive Assessment*, AF: Atrial Fibrillation

were common, as were overlapping deficits across multiple cognitive subdomains.<sup>11</sup>

In- this study there was no statistically significant difference in cognitive function between paroxysmal and persistent AF patients. This condition was also failed to be shown in some previous studies, although

some clinical parameters showed differences between the two groups.<sup>12,13</sup> On the contrary, several previous studies had found significant differences in cognitive function between patients with paroxysmal and persistent AF, but with different cognitive examinations.<sup>6,14,15</sup>

These different results might be causes

by several things i.e differences in the characteristics of the subjects, differences in the methodology, differences in cognitive function tests and differences in other comorbidities that can also affect cognitive function. In this study, between the two AF groups there were significant differences in two variables of clinical characteristics i.e the anticoagulant therapy and comorbidity of type 2 DM (Table 1). These two variables in the paroxysmal AF group could cause more severe cognitive impairment than they should be.

The majority of subjects in this study, especially the paroxysmal AF group, received less anticoagulant therapy and did not achieved therapeutic INR range so that they were at high risk for thromboembolism, including microemboli which could cause microinfarct in the brain, leading a cognitive impairment. This was in accordance with several previous studies, who stated that anticoagulant therapy and therapeutic INR were important to prevent embolism.<sup>16,17</sup> Futhermore, there was more comorbidity of type 2 DM in the paroxysmal AF group, where as it was known that AF patients who had type 2 DM comorbidity would have a higher tendency for cerebral ischemic which of course will have a negative impact on cognitive function, as showed in some previous studies.<sup>18,19</sup>

However, subsequent analysis of these two variables, both with multiple regressions (with adjusted) and other subanalysis, showed that there were no significant effects of these two variables on the analysis of the comparison of MoCA-Ina scores between the paroxysmal and persistent AF groups, even though the characteristics of the two variables significantly different between the two groups. One reason that can be considered is whether there are differences in the characteristics of anticoagulant therapy and comorbidity of type 2 DM variables which have not been further evaluated in this study such as the small number of samples with type 2 DM comorbidity, the effect of type 2 DM treatment and glycemic control, duration of drug use, compliance, the type of drug, the effectiveness and drug interactions that might be different in the two AF groups thus affecting the results of this study.

The results of several additional analyses above, most likely indeed illustrate that in this study most patients in the paroxysmal AF group had cognitive decline as well as in the persistent AF group. Although not in line

with the differences in the pathophysiology of thrombus formation described previously, this is still possible because both groups have a median CHA<sub>2</sub>DS<sub>2</sub>-VASc score =3 which means that they have a high risk of thromboembolism/microembolism as well as the risk of SCI. Several studies linking CHA<sub>2</sub>DS<sub>2</sub>-VASc scores with cognitive impairment, reported a 2-fold increased risk of cognitive decline in patients with a score of  $\geq 3$ .<sup>2,11</sup> Nowadays screening and administration of anticoagulants in AF patients is not based on AF type but based on thromboembolic risk, one of which is using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>20</sup> Many guidelines have recommended the administration of anticoagulants for paroxysmal AF patients with the same criteria as those applied to persistent AF patients.<sup>21</sup>

By assuming that cognitive impairment is a predictor of SCI in paroxysmal AF patients, it is expected that different approaches can be given for the management of paroxysmal AF patients, such as periodic cognitive function screening, neuroimaging examination to see lesions of SCI and most importantly, early anticoagulant therapy can be given to the patients with impaired cognitive function even though the CHA<sub>2</sub>DS<sub>2</sub>-VASc score <2.

In addition to SCI, several other mechanisms need to be considered as the pathophysiology that causes cognitive impairment in AF patients, such as cerebral hypoperfusion and vascular inflammation.<sup>4</sup> However, there has been no studies that specifically analyzed them in paroxysmal and persistent AF patients. Furthermore, this study also did not collect and analyze variables that might be different in the two AF groups based on the above mechanisms, such as measurement of cardiac output or cardiac index which could be indicators of cerebral hypoperfusion or measurement of inflammatory mediators that could support the presence of vascular inflammation.

In conclusion, cognitive function in paroxysmal AF patients did not show differences with persistent AF patients in terms of MoCA-Ina total score and MoCA-Ina cognitive subdomain score. Both AF groups had lower cognitive function than the general population without AF. Therefore, it is important to screen cognitive function in all AF patients using the MoCA-Ina test, besides that it is necessary to consider giving anticoagulants for the prevention of stroke or SCI in AF patients.

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