Oraby *et al.*
Egypt J Neurol Psychiatry Neurosurg (2023) 59:57
https://doi.org/10.1186/s41983-023-00660-4

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

Open Access

The negative impact of atrial fibrillation, and other common cardiac risk factors on cognition

Mohammed I. Oraby[1], Rasha H. Soliman[1], Mona Hussein[1], Hanan Mohamed M. Ibrahim[1] and Noha A. Abd ElMonem[1*]

Abstract

Background Accumulating evidence has suggested that atrial fibrillation might play a role in the pathogenesis of vascular cognitive impairment. The aim of this study was to evaluate the cognitive functions and to determine the pattern of cognitive impairment in stroke-free patients, with AF and other cardiac risk factors (pulmonary hypertension and diastolic dysfunction). 55 patients, diagnosed with AF and 40 matched normal controls underwent psychometric tests, including the Modified Mini-Mental State examination test, PALT test, BVRT test, Token test, Trail B test, and PASAT test. MRI of the brain was performed for the patients to exclude brain infarction and a cardiological assessment included electrocardiography and echocardiogram. All patients had confirmed diagnosis of AF in the last 12 months and 43 patients had pulmonary hypertension.

Results AF patients had significant impairment (*p*-value 0.009) in different cognitive domains (verbal, visual memory and working memory), compared to controls. Patients with pulmonary hypertension had a significant impairment in receptive language skills, working memory, attention, and arithmetic capabilities.

Conclusion AF stroke-free patients and patients with pulmonary hypertension had significant impairment in different cognitive domains.

Keywords Atrial fibrillation, Cardiac risk factors, Cognitive domains, Vascular cognitive impairment

Background

Vascular cognitive impairment (VCI) includes the cognitive changes related to cerebrovascular diseases. And refers to the wide spectrum of behavioral and cognitive impairment ranging from early cognitive decline to clear dementia with the affection of attention and executive functions [1].

It has been identified with the white matter lesions on brain imaging. These changes increase with age and correlate negatively with cognitive function. Vascular cognitive impairment has been associated with sizable cerebral infarction, multiple lacunar infarctions, and/or small vessel disease which may be detected by MRI. A negative correlation was found between the degree of such changes in MRI and cognitive functions [2].

Proposed mechanisms by which AF can produce cognitive impairment are now elucidated [3]. AF is found to be related to high incidence of silent cerebral infarcts and cerebral microbleeds. Also, a pro-inflammatory state, in those patients may play a role. Different studies indicate that medications of anticoagulation can lower the risk of cognitive deterioration in AF patients. Furthermore, more cerebral lesions due to catheter ablation are increasingly documented [4]. Revealing the pathogenesis of the cognitive changes and dementia in patients with AF can help to make protective strategies [5]. Different

*Correspondence:
Noha A. Abd ElMonem
nohaaliaelmonem@yahoo.com
[1] Department of Neurology, Beni-Suef University, Beni-Suef 62511, Egypt

studies suggest that hypoxia and consequent tauopathies (neurodegenerative diseases associated with pathological tau protein), leading to AD and other neurodegenerative disorders [6].

This work aimed to determine the cognitive function in patients with AF in stroke-free patients and to assess the negative impact of other common cardiac risk factors on cognition.

Methods

The present study is a case–control study, conducted on 55 patients diagnosed as having AF and 40 healthy controls, matched for age and sex. A battery of psychometric studies were done, investigating the negative impact of common cardiac risk factors on cognition. All patients included in this study had confirmed electrocardiographic (ECG) diagnosis of AF in the last 12 months (paroxysmal, persistent, or permanent). The exclusion criteria for the patients included the following; subjects with linguistic troubles or any medical illness interfering with complete testing, subjects with a previous history of cerebrovascular stroke, myocardial infarction, or heart failure, and subjects with a history of alcohol, substance or drug abuse with cognitive side effects as anti-epileptic, or anti-cholinergic, subjects with MRI brain showing structural lesions like infarctions, intra-cerebral hemorrhage, subdural hematoma, tumors, hydrocephalus or cerebral venous thrombosis.

The included patients underwent the following: clinical assessment including a medical and neurological examination. A battery of psychometric tests including; (1) the Modified Mini-Mental State examination test (3MS): it is a new version of the MMSE, designed for assessment of temporal and spatial orientation, the capability to see relations between objects, memory and verbal fluency [7]. (2) Paired Associate Learning Test (PALT): this test is used to evaluate verbal memory, based on semantic cueing [8]. (3) Benton Visual Retention Test (BVRT): for evaluation of visual (perceptual, memory, motor) and visuoconstructive abilities [9]. (4) Token Test: it is used to evaluate receptive language skills [10]. (5) Trail B Test: it is used for evaluation of executive function, attention and psychomotor speed. The test is composed of 2 parts. In our study, we used the total score of Trail B Test only [11]. (6) Paced Auditory Serial Addition Test (PASAT): it is used for evaluation of attention, working memory, and arithmetic capabilities [12]. Cardiological assessment done by cardiology specialist and included electrocardiography (ECG): using 12 leads standard electrocardiogram (Mindray_BeneHeartR3A) and echocardiogram: two-dimensional echocardiography was carried out using Vivid S5 N (GE Vingmed ultrasound as strandpromenaden 45, N-3191 Horten, Norway). Hamilton Depression Scale was done to exclude depression; all participants included in this study had a score of 0–7. Also, all the patients underwent MRI brain to exclude any structural brain lesion that could account for cognitive impairment. This study was approved by the Ethical Committee in the Faculty of medicine, (FWA00015574). Written informed consent was signed by the patients after explanation of the aim of the study.

Statistical analysis

Statistical Package for the Social Sciences was used to code and enter the data (SPSS v 20). Quantitative variables were reported using mean and standard deviations, while qualitative variables were reported using frequencies (number) and relative frequencies (percent). Student's t-tests and Chi-square tests were used to compare patients and the control group. Significant was defined as a p-value of less than or equal to 0.05.

Results

The mean age in our patients was 44.47 years with a standard deviation of 11.32 years, while the mean value for age in controls was 39.58 years with a standard deviation of 12.8 years. In the present study, 67.3% ($n=37$) of the patients were females and 32.7% ($n=18$) were males. As regards controls, 60% ($n=24$) were females and 40% ($n=16$) were males. Regarding age and gender distribution, there was no statistically significant difference between patients and controls.

According to the results of the psychometric tests, no statistical difference was found between patients and controls in the Modified Mini-Mental State (3MS), Trail B Test, and Token Test (Table 1). Comparing the two groups, a statistically significant difference was found in (PALT), (PASAT), and (BVRT) (Fig. 1).

According to the echocardiographic assessment, 83.6% ($n=46$) of patients had valvular heart disease. 61.8% ($n=34$) of the patients had left atrium dilatation and

Table 1 Cognitive assessment in patients and control groups

	Patients ($n=55$) Mean ± SD	Controls ($n=40$) Mean ± SD	*P*-value
3MS	99.13 ± 1.47	99.08 ± 1.25	0.856
Trail Making B	122.93 ± 44.65	110.33 ± 45.94	0.183
Token	158.11 ± 7.49	158 ± 7.2	0.943
PALT	14.92 ± 3.03	16.51 ± 2.69	0.009*
PASAT	45.55 ± 20.37	54.08 ± 13.32	0.016*
BVRT	19.35 ± 3.74	21 ± 2.96	0.023*

3MS Modified Mini-Mental State Examination Test, *PALT* Paired Associate Learning Test, *PASAT* Paced Auditory Serial Addition Test, *BVRT* Benton Visual Retention Test

*P-value ≤ 0.05 (significant)

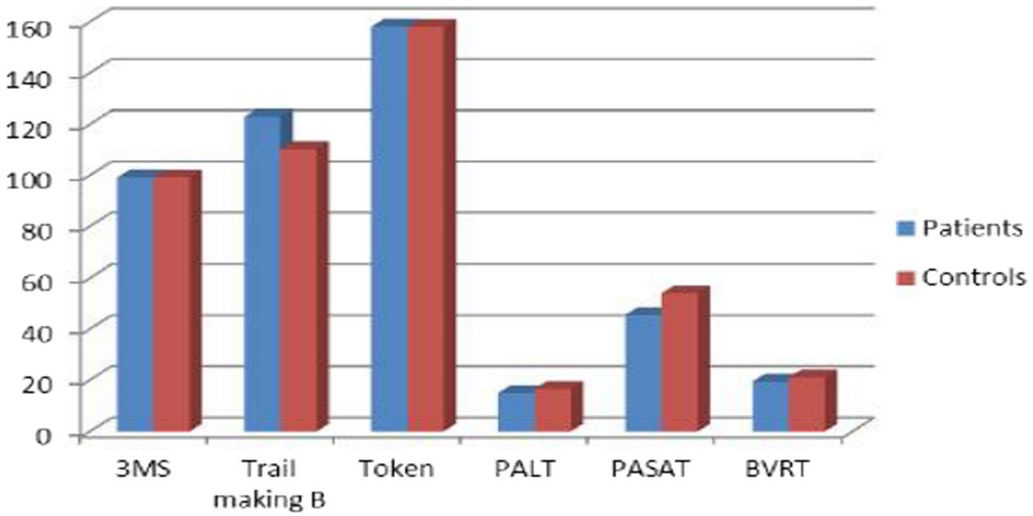

Fig. 1 Cognitive assessment in patients and control groups

Table 2 Comparison between patients with and without left atrium dilatation regarding cognitive function assessment

	Patients with LT atrium dilatation (*N*) Mean ± SD	Patients without LT atrium dilatation (*N*) Mean ± SD	*P*-value
3MS	99.26 ± 0.79	98.9 ± 2.17	0.381
Trail Making B	121.82 ± 48.94	124.7 ± 37.74	0.818
Token	158.15 ± 7.83	158.05 ± 7.08	0.962
PALT	15.16 ± 3.17	14.52 ± 2.83	0.454
PASAT	44.53 ± 20.99	47.19 ± 19.72	0.642
BVRT	19.47 ± 3.82	19.14 ± 3.71	0.756

3MS Modified Mini-Mental State Examination Test, *PALT* Paired Associate Learning Test, *PASAT* Paced Auditory Serial Addition Test, *BVRT* Benton Visual Retention Test

P-value ≤ 0.05 (significant)

Table 3 Comparison between patients with and without diastolic dysfunction regarding cognitive function assessment

	Patients with diastolic dysfunction (*N*) Mean ± SD	Patients without diastolic dysfunction (*N*) Mean ± SD	*P*-value
3MS	99.32 ± 0.85	98.97 ± 1.83	0.379
Trail Making B	131.24 ± 51.69	116 ± 37.31	0.21
Token	156.76 ± 9.44	159.23 ± 5.27	0.251
PALT	15.24 ± 3.05	14.65 ± 3.04	0.478
PASAT	43.04 ± 20.71	47.63 ± 20.19	0.41
BVRT	19 ± 4.15	19.63 ± 3.41	0.537

3MS Modified Mini-Mental State Examination Test, PALT Paired Associate Learning Test, PASAT Paced Auditory Serial Addition Test, BVRT Benton Visual Retention Test

P-value ≤ 0.05 (significant)

78.2% ($n=43$) of the patients had pulmonary hypertension. Cardiomyopathy was not detected in any of the included patients.

Comparing patients with and without left atrium dilatation, no statistically significant difference regarding Modified Mini-Mental State 3MS, Trail Making B, Token, PALT, PASAT, and BVRT (Table 2).

No statistically significant difference was found between patients with and without diastolic dysfunction in 3MS, Trail Making B, Token, PALT, PASAT, and BVRT (Table 3).

Comparing patients with and without valvular heart disease, there was no statistically significant difference in 3MS, Trail Making B, Token, PALT, and BVRT. While a statistically significant difference was found between those with and without valvular heart disease in PASAT (Table 4). While the results were statistically significant, smaller difference between both sample size may improve the results.

A statistically significant difference was found between patients with and without pulmonary hypertension in Trail Making B, Token, and PASAT (Table 5).

AF patients had significant impairment in verbal and visual memory attention, working memory, and arithmetic capabilities according to PALT, PASAT, and BVRT compared to controls. Also, a statistically significant difference was found between patients with and without pulmonary hypertension in executive function,

Table 4 Comparison between patients with and without valvular heart disease regarding cognitive function assessment

	Patients with valvular heart disease (*n*:46) Mean ± SD	Patients without valvular heart disease (*n*:9) Mean ± SD	*P*-value
3MS	99.07 ± 1.57	99.44 ± 0.73	0.483
Trail Making B	124.39 ± 46.72	115.44 ± 33.23	0.587
Token	157.91 ± 7.42	159.11 ± 8.22	0.665
PALT	14.89 ± 3.18	15.06 ± 2.28	0.883
PASAT	43.39 ± 21.21	56.56 ± 10.33	0.009*
BVRT	19.22 ± 3.91	20 ± 2.83	0.571

3MS Modified Mini-Mental State Examination Test, *PALT* Paired Associate Learning Test, *PASAT* Paced Auditory Serial Addition Test, *BVRT* Benton Visual Retention Test

**P*-value 0.05 (significant)

Table 5 Comparison between patients with and without pulmonary hypertension regarding cognitive function assessment

	Patients with pulmonary hypertension (*n*:43) Mean ± SD	Patients without pulmonary hypertension (*n*:12) Mean ± SD	*P*-value
3MS	98.98 ± 1.6	99.67 ± 0.65	0.151
Trail Making B	131.7 ± 46.49	91.5 ± 12.48	0.000*
Token	157.14 ± 8.12	161.58 ± 2.58	0.003*
PALT	14.59 ± 3.14	16.08 ± 2.36	0.133
PASAT	42.63 ± 21.05	56 ± 13.86	0.015*
BVRT	19.05 ± 4.02	20.42 ± 2.31	0.266

3MS Modified Mini-Mental State Examination Test, *PALT* Paired Associate Learning Test, *PASAT* Paced Auditory Serial Addition Test, *BVRT* Benton Visual Retention Test

**P*-value 0.05 (significant)

attention, psychomotor speed, receptive language skills, attention, working memory, and arithmetic capabilities.

Discussion

AF is a well-documented modifiable risk factor for stroke, and can be a predictor for vascular cognitive impairment and dementia which can occur not only due to clinically recognized strokes, but also through silent brain infarcts, microinfarcts, and small vessel disease which can be detected by neuroimaging [13, 14]

This study aimed to determine the negative impact of AF and other common cardiac risk factors in stroke-free patients on cognition.

In the present study, AF patients had significant impairment in verbal and visual memory attention, working memory, and arithmetic capabilities according to PALT, PASAT, and BVRT compared to controls.

Similar to our findings, [15] found a significant impairment in cognitive domains in AF patients, in comparison to controls. Cognitive function was assessed with the adjusted Mini-Mental State Examination score and Memory and Executive Screening (MES) score. [16] assessed cognitive function by the Montreal Cognitive Assessment Battery, depression, and anxiety in AF patients. Depression was the most commonly documented in almost half of the patients. Nearly one-third of participants had cognitive impairment.

[17] found that AF was a predictor of a faster global cognitive impairment in the elderly. [18, 19] detected more impairment in global cognitive function in AF patients than in controls.

Proposed mechanisms by which AF can produce cognitive impairment include; altered cerebral blood flow, cerebral hypo perfusion, cerebral micro-emboli, microbleeds, cerebral small vessel diseases, vascular inflammation, and in the end brain atrophy [3].

The cognitive dysfunction in patients with AF may also be attributed to the presence of silent cerebrovascular lesions. Due to low cardiac output in those patients, they are susceptible to lower cerebral perfusion, and, to thromboembolism associated with blood stasis and systemic hypercoagulable state [20].

Compared with controls with sinus rhythm, cerebral ischemia (CI) was shown to be 2 to 7 times more common in patients with persistent or paroxysmal AF [21]. Reduced cardiac output in patients with AF was found to be the pathological mechanism that leads to reduced cerebral blood flow, particularly to the temporal lobes; thus, increasing the incidence of dementia [22].

Dementia in AF may also be linked to inflammation and genetic factors [23]. Interleukin-6 and C-reactive protein are serological biomarkers that can be used as predictors of AF after being adjusted for any associated cardiovascular diseases [24]. In some AF patients, microbleeds due to anticoagulation therapy could explain the progressive cognitive decline related to those patients [25]. On the other hand, [26, 27] revealed no significant difference in cognitive function between patients with AF and controls. Longitudinal studies and follow-up of age matched patients and controls may be needed to exclude that cognitive changes may be attributed to the age.

In our study, there were statistically significant differences between patients with and without valvular heart diseases in the following cognitive domains: attention, working memory, and arithmetic capabilities. While better results may need smaller difference between patient and control groups.

Similar to our findings, [28] reported a marked aortic and mitral valve disease in patients with dementia compared to non-demented control. [29] suggested

that, in addition to AF, left atrial dysfunction increased with chronic mitral valve disease, so increasing the risk of cognitive decline. Heart disease and its associated reduced cerebral blood flow (CBF), affects the vascular homeostasis of the brain, builds tau and Aβ proteins and consequently, cognitive impairment symptoms follow.

In the present study, a statistically significant difference was found between patients with and without pulmonary hypertension in executive function, attention, psychomotor speed, receptive language skills, attention, working memory, and arithmetic capabilities.

Similarly, comparing patients with pulmonary hypertension and controls, [30] found a statistically significant difference in cognitive function between both groups. Cognitive testing was done on the patients at baseline and after 3 months. Cognitive domains showed an improvement after 3 months of disease-targeted therapy. This might improve cerebral oxygen delivery secondary to better hemodynamics.

White et al. [31] found that patients with pulmonary hypertension had significant cognitive impairments, depression, and decreased quality of life. [32–34] recorded that patients with pulmonary hypertension had more hypoxia and lower cerebral blood flow compared to healthy participants, suggesting that the first pathological mechanism involved in cognitive dysfunction in those patients, is impairment of cerebral blood flow.

Malenfant et al., Cunningham et al., and Hu et al. [35–37] reported other pathological mechanisms in patients with pulmonary hypertension include neuroinflammation, impaired cerebral hemodynamic regulation and neurodegenerative factors dysregulation.

In the present study, there was no statistically significant difference in cognitive function between patients with and without left atrial dilatation in any of the tested cognitive domains.

In contrast to our study, [38] reported a link between LAE and cognitive decline. Additionally, [38] found a statistically significant difference in cognitive function between AF patients with LT atrial dilatation and patients without AF and with normal LA size. Surprisingly, after a follow-up of 5 years, these patients (with LAE and AF) did not manifest more cognitive changes, compared with the other group.

Alosco et al. [39] suggested that LA dilatation is linked to cognitive decline in the elderly. This may be explained by the sensitivity of LA size to underlying CVD severity, as it is associated with abnormalities in diastolic filling and consequently LV diastolic pressure.

This controversy needs follow-up studies. Microstructural changes through radiological studies of the brain may help. Also, the role of atrial natriuretic peptide, a hormone commonly linked with cognitive function, should be clarified.

In the present study, there was no statistically significant correlation between diastolic dysfunction and cognitive impairment in patients with AF in any of the tested cognitive domains.

Similar to our findings, [40] concluded that there was no significant relationship between diastolic dysfunction and cognitive impairment when investigating the echocardiography parameters and cognitive domains, using neuropsychiatric screening tools and neuropsychological tests.

On the other hand, [41] found a significant correlation between diastolic dysfunction and MCI. Patients with LV diastolic dysfunction revealed odds of concurrent MCI that was about two times higher than for participants with normal cardiac assessment, even after adjustment of different clinical parameters.

Park et al. [42] found a strong correlation between LV diastolic function and working memory, fluency, visual memory, and processing speed.

This contrast of the results may be due to impaired hemodynamics. Hypoxia leads to decreased volume of both the whole brain and, brain cognitive areas (the hippocampus and frontal cortex). Changes in blood flow also affect the highly sensitive white matter watershed areas of the brain [43].

Small number of patients due to financial issues and limitation of resources. Longitudinal studies with follow-up brain imaging considering the cardiac risk factor profile-to investigate their role on cognition—are highly recommended. More researches about the relationship between different cardiac diseases and microstructure changes of the brain should be conducted, considering the role of cardiac disease medications.

Conclusion

AF stroke-free patients had significant impairment in different cognitive domains. Verbal and visual memory, working memory, attention, and arithmetic capabilities are the most commonly affected. Also, a statistically significant difference was detected between patients with and without pulmonary hypertension in executive function, attention, psychomotor speed, receptive language skills, attention, working memory, and arithmetic capabilities.

Abbreviations

AF	Atrial fibrillation
VCI	Vascular cognitive impairment
MRI	Magnetic resonance imaging
ECG	Electrocardiography
3MS	The Modified Mini-Mental State Examination Test
MMSE	Mini-Mental State Examination

PALT	Paired Associate Learning Test
BVRT	Benton Visual Retention Test
PASAT	Paced Auditory Serial Addition Test
ME	Memory and Executive Screening score
CBF	Cerebral blood flow
LAE	Left atrial enlargement
CI	Cerebral ischemia
CVD	Cerebrovascular disease
LV	Left ventricular
MCI	Mild cognitive impairment

Acknowledgements
Not applicable.

Author contributions
MO participated in study design, sequence alignment, analysis of data, and helped to draft the manuscript. RS participated in study design, sequence alignment, and analysis of data and helped to draft the manuscript.MH participated in the study design, collection, and analysis of data and helped to draft the manuscript.HM participated in the study design, and analysis of data and helped to draft the manuscript. NA participated in the study design, and analysis of data and helped to draft the manuscript. All authors read and approved the final manuscript.

Funding
The authors did not receive any funding for this work.

Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request with permission of the Faculty of Medicine, Beni-Suef University, Egypt.

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from each participant in this study and the study was approved by the authorized ethical committee in the Faculty of Medicine, Beni-Suef University (FWA00015574).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 24 January 2023 Accepted: 11 April 2023
Published online: 28 April 2023

References

1. van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, et al. Vascular cognitive impairment. Nat Rev Dis Primers. 2018;15(4):18003.
2. Pozorski V, Oh JM, Okonkwo O, Krislov S, Barzgari A, Theisen F, et al. Cross-sectional and longitudinal associations between total and regional white matter hyperintensity volume and cognitive and motor function in Parkinson's disease. Neuroimage Clin. 2019;23: 101870.
3. Sepehri Shamloo A, Dagres N, Müssigbrodt A, Stauber A, Kircher S, Richter S, et al. Atrial fibrillation and cognitive impairment: new insights and future directions. Heart Lung Circ. 2020;29(1):69–85.
4. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. Nat Rev Cardiol. 2018;15(12):744–56.
5. Norris D, Clark MS, Shipley S. The mental status examination. Am Fam Physician. 2016;94(8):635–41.
6. Hachinski V, Einhäupl K, Ganten D, Alladi S, Brayne C, Stephan BCM, et al. Preventing dementia by preventing stroke: the Berlin Manifesto. Alzheimers Dement. 2019;15(7):961–84.
7. Zhang F, Niu L, Li S, Le W. Pathological impacts of chronic hypoxia on Alzheimer's disease. ACS Chem Neurosci. 2019;10(2):902–9.
8. Inglis J. A paired-associate learning test for use with elderly psychiatric patients. J Ment Sci. 1959;105(439):440–3.
9. Manna CG, Alterescu K, Borod JC, Bender HA. Benton visual retention test. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of clinical neuropsychology. New York: Springer; 2011. p. 392–4.
10. De Renzi E, Vignola LA. The token test: a sensitive test to detect receptive disturbances in aphasics. Brain. 1962;85:665–78.
11. Kalbe E, Bintener C, Ophey A, Reuter C, Gobel S, Klöters S, et al. Computerized cognitive training in healthy older adults: baseline cognitive level and subjective cognitive concerns predict training outcome. Health. 2018;10:20–55.
12. Tombaugh TN. A comprehensive review of the paced auditory serial addition test (PASAT). Arch Clin Neuropsychol. 2006;21(1):53–76.
13. Pastori D, Miyazawa K, Lip GYH. Dementia and atrial fibrillation: a dangerous combination for ischemic stroke and mortality. J Alzheimers Dis. 2018;61(3):1129–32.
14. Wang Z, Lin Y, Liu Y, Chen Y, Wang B, Li C, et al. Serum uric acid levels and outcomes after acute ischemic stroke. Mol Neurobiol. 2016;53(3):1753–9.
15. Xiong N, Shen J, Wu B, Yan P, Shi H, Li J, et al. Factors influencing cognitive function in patients with atrial fibrillation: a cross-sectional clinical study. J Int Med Res. 2019;47(12):6041–52.
16. Bostrom JA, Saczynski JS, Hajduk A, Donahue K, Rosenthal LS, Browning C, et al. Burden of Psychosocial and Cognitive Impairment in Patients With Atrial Fibrillation. Crit Pathw Cardiol. 2017;16(2):71–5.
17. Ding M, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, et al. Atrial fibrillation, antithrombotic treatment, and cognitive aging: a population-based study. Neurology. 2018;91(19):e1732–40.
18. Kawabata-Yoshihara LA, Scazufca M, Santos Ide S, Whitaker A, Kawabata VS, Benseñor IM, et al. Atrial fibrillation and dementia: results from the Sao Paulo ageing & health study. Arq Bras Cardiol. 2012;99(6):1108–14.
19. Di Nisio M, Prisciandaro M, Rutjes AW, Russi I, Maiorini L, Porreca E. Dementia in patients with atrial fibrillation and the value of the Hachinski ischemic score. Geriatr Gerontol Int. 2015;15(6):770–7.
20. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. Can J Cardiol. 2017;33(12):1556–64.
21. Haeusler KG, Wilson D, Fiebach JB, Kirchhof P, Werring DJ. Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives. Heart. 2014;100(18):1408–13.
22. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. J Am Coll Cardiol. 2019;73(5):612–9.
23. Chung MK, Eckhardt LL, Chen LY, Ahmed HM, Gopinathannair R, Joglar JA, et al. American Heart Association Electrocardiography and Arrhythmias Committee and Exercise, Cardiac Rehabilitation, and Secondary Prevention Committee of the Council on Clinical Cardiology; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; and Council on Lifestyle and Cardiometabolic Health. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. Circulation. 2020;141(16):e750-e772.
24. Lane DA, Boos CJ, Lip GY. Atrial fibrillation (chronic). BMJ Clin Evid. 2015;20(2015):0217.
25. Poels MM, Ikram MA, van der Lugt A, Hofman A, Niessen WJ, Krestin GP, et al. Cerebral microbleeds are associated with worse cognitive function: the Rotterdam Scan Study. Neurology. 2012;78(5):326–33.
26. Rastas S, Verkkoniemi A, Polvikoski T, Juva K, Niinistö L, Mattila K, et al. Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. Stroke. 2007;38(5):1454–60.
27. Pulignano G, Del Sindaco D, Tinti MD, Tolone S, Minardi G, Lax A, et al. Atrial fibrillation management in older heart failure patients: a complex clinical problem. Heart Int. 2016;11(1):e41–9.
28. Corder EH, Ervin JF, Lockhart E, Szymanski MH, Schmechel DE, Hulette CM. Cardiovascular damage in Alzheimer disease: autopsy findings from the Bryan ADRC. J Biomed Biotechnol. 2005;2005(2):189–97.
29. Boudoulas KD, Sparks EA, Rittgers SE, Wooley CF, Boudoulas H. Factors determining left atrial kinetic energy in patients with chronic mitral valve disease. Herz. 2003;28(5):437–44.
30. Somaini G, Stamm A, Müller-Mottet S, Hasler E, Keusch S, Hildenbrand FF, et al. Disease-targeted treatment improves cognitive function

in patients with precapillary pulmonary hypertension. Respiration. 2015;90(5):376–83.
31. White J, Hopkins RO, Glissmeyer EW, Kitterman N, Elliott CG. Cognitive, emotional, and quality of life outcomes in patients with pulmonary arterial hypertension. Respir Res. 2006;7(1):55.
32. Yuan P, Li J, Liu J, Liu H, Gong S, Wang L, et al. Cognitive dysfunction in patients with pulmonary hypertension. Am J Respir Crit Care Med. 2022;206(10):1289–93.
33. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet. 2017;390(10113):2673–734.
34. Honarmand K, Lalli RS, Priestap F, Chen JL, McIntyre CW, Owen AM, et al. Natural history of cognitive impairment in critical illness survivors. A systematic review. Am J Respir Crit Care Med. 2020;202(2):193–201.
35. Malenfant S, Brassard P, Paquette M, Le Blanc O, Chouinard A, Bonnet S, et al. Continuous reduction in cerebral oxygenation during endurance exercise in patients with pulmonary arterial hypertension. Physiol Rep. 2020;8(6): e14389.
36. Cunningham CM, Li M, Ruffenach G, Doshi M, Aryan L, Hong J, et al. Y-chromosome gene, uty, protects against pulmonary hypertension by reducing proinflammatory chemokines. Am J Respir Crit Care Med. 2022;206(2):186–96.
37. Hu L, Wang J, Huang H, Yu Y, Ding J, Yu Y, et al. YTHDF1 regulates pulmonary hypertension through translational control of MAGED1. Am J Respir Crit Care Med. 2021;203(9):1158–72.
38. Zhang MJ, Norby FL, Lutsey PL, Mosley TH, Cogswell RJ, Konety SH, et al. Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: the ARIC-NCS. J Am Heart Assoc. 2019;8(23): e013197.
39. Alosco ML, Gunstad J, Jerskey BA, Clark US, Hassenstab JJ, Xu X, et al. Left atrial size is independently associated with cognitive function. Int J Neurosci. 2013;123(8):544–52.
40. Hashemi M, Jervekani ZT, Mortazavi S, Maracy MR, Barekatain M. Association between cognitive function and parameters of echocardiography and coronary artery angiography. Arq Neuropsiquiatr. 2018;76(4):225–30.
41. Sacre JW, Ball J, Wong C, Chan YK, Stewart S, Kingwell BA, et al. Mild cognitive impairment is associated with subclinical diastolic dysfunction in patients with chronic heart disease. Eur Heart J Cardiovasc Imaging. 2018;19(3):285–92.
42. Park CM, Williams ED, Chaturvedi N, Tillin T, Stewart RJ, Richards M, et al. Associations between left ventricular dysfunction and brain structure and function: findings from the SABRE (Southall and Brent Revisited) study. J Am Heart Assoc. 2017;6(4): e004898.
43. Bratzke-Bauer LC, Pozehl BJ, Paul SM, Johnson JK. Neuropsychological patterns differ by type of left ventricle dysfunction in heart failure. Arch Clin Neuropsychol. 2013;28(2):114–24.

Publisher's Note