CLINICAL REVIEW

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Revitalizing brain perfusion: Unveiling advancements through rhythm control strategies in atrial fibrillation—A systematic review

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Abstract

Background: Recent evidence suggests an elevated risk of cognitive impairment and dementia in individuals with atrial fibrillation (AF), irrespective of stroke occurrence. AF, known to reduce brain perfusion, particularly through silent cerebral ischemia, underscores the intricate relationship between cardiac and cerebral health. The heart plays a crucial role in supporting normal brain function, and rhythm control, a standard AF treatment, has demonstrated enhancements in brain perfusion. This systematic review aimed to examine published data concerning the influence of rhythm control on brain perfusion in patients with atrial fibrillation.

Methods: A systematic search for relevant studies was carried out in Scopus, PubMed, Cochrane Reviews, ProQuest, and EBSCOhost, spanning from their inception until April 30, 2023. Studies that specifically examined brain perfusion following any form of rhythm control in atrial fibrillation were included in the review.

Results: The review encompassed 10 studies involving 436 participants. Among these, six utilized electrical cardioversion for rhythm control. The majority (8 out of 10) demonstrated that restoring sinus rhythm markedly enhances brain perfusion. In one of the two remaining studies, notable improvement was observed specifically in a region closely linked to cognition. Additionally, both studies reporting data on the Mini-Mental State Examination (MMSE) showed a consistent and significant increase in scores following rhythm control.

Conclusion: Successful rhythm control in AF emerges as a significant contributor to enhanced brain perfusion, suggesting a potential therapeutic avenue for reducing cognitive impairment incidence. However, further validation through larger prospective studies and randomized trials is warranted.

KEYWORDS
atrial fibrillation, brain perfusion, cardioversion, cerebral blood flow, rhythm control

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most common heart rhythm disorders. The incidence and prevalence of AF have tripled globally in the last 5 years and have reached the dimension of a 21st-century cardiovascular disease epidemic.[1–3]

There is growing interest in exploring the potential connection between atrial fibrillation and cognitive decline as well as dementia.[4] Numerous studies over the past decade, including several meta-analyses, provide growing evidence that patients with atrial fibrillation are at increased risk for cognitive impairment and dementia, even in the absence of stroke.[5–10] Whether the link is causal is still an open question.[5] It is intuitive to perceive the link between those conditions and brain hypoperfusion as an underlying mechanism.[11]

AF is known to reduce brain perfusion, and silent cerebral ischemia is considered the main mechanism for increasing cognitive risk.[12] The study of brain perfusion is crucial for gaining essential insights into the functioning of the central nervous system.[13] It helps us comprehend dysfunction in the brain, which is a leading cause of morbidity and mortality in Western societies.[13] The intricate mechanisms of human cerebral circulation have attracted global research interest.[14] Dysfunction of one or more of these mechanisms may contribute to the adverse brain events associated with AF.[15]

The brain receives 15% of total cardiac output and is highly dependent on the normal functioning of the heart.[16] When atrial fibrillation develops, there is a loss of atrial transport factor ("atrial kick") leading to a decrease in cardiac output of up to 20%–30%.[17] Evidence suggests that altered cardiac output, acute or chronic, leads to changes in cerebral circulation independently of other regulating parameters such as blood pressure and carbon dioxide levels.[18] Ensuring brain perfusion is a priority during acute reductions in cardiac output.[18]

Rhythm control has been widely known as one of the main strategies to treat AF. It was shown that cardioversion to sinus rhythm (SR) improves brain perfusion.[19] Nevertheless, the evidence remains inconclusive regarding a direct causal effect. This systematic review aimed to assess whether rhythm control in atrial fibrillation plays a role in brain perfusion.

2 | METHODS

This systematic review followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[20] and was registered in the PROSPERO database with registration number CRD42023414229. This systematic review adheres to the PRISMA checklist, as detailed in Table S3, to ensure transparent reporting.

2.1 | Search strategy

A systematic search for eligible studies was conducted independently by two authors, SR and AN, in Scopus, PubMed, Cochrane Reviews, ProQuest, and EBSCOhost databases from inception until April 30,

2023. The research question is given as follows: "In patients with atrial fibrillation, does rhythm control result in improvements of brain perfusion when compared with before or without rhythm control?" Brain perfusion is often quantified by cerebral blood flow (CBF), indicating the volume of blood passing through brain tissue per unit of time (typically expressed as mL/100 g of brain tissue/min).[13] CBF is regulated by the careful interaction of chemical, metabolic, autoregulatory, neural, and systemic factors.[15] However, measuring CBF directly in clinical settings is challenging, leading to the development of various methods, from minimal to highly invasive.[13] Assessment of brain saturation is more frequently performed.[21] Prior studies have indicated a correlation between brain saturation and either brain perfusion or cognitive dysfunction.[21] Thus, the following keywords were used: "((rhythm control) OR (cardioversion) OR (ablation) OR (rate control)) AND ((atrial fibrillation) OR (afib) OR (af)) AND ((brain perfusion) OR (cerebral perfusion) OR (cerebral blood flow) OR (cerebral oxygen saturation) OR (brain saturation))."

2.2 | Eligibility criteria

Studies focusing on brain perfusion after any rhythm control in atrial fibrillation were considered. The eligibility criteria included the following: (1) involving human participants diagnosed with atrial fibrillation, (2) involving patients receiving any rhythm control strategies, (3) reporting any measurement depicting brain perfusion before and after rhythm control, (4) a retrospective or prospective cohort, cross-sectional, or randomized controlled trial (RCT) study, and (5) full text available in English language. Studies that failed to fulfill the eligibility criteria were excluded.

2.3 | Study selection and data extraction

Five authors, SR, AS, AN, MA, and RY, performed screening and selecting studies from all databases for inclusion independently. The decision is not visible to other reviewers (blinded) and is gathered altogether via Rayyan Systems Inc. A minimum of 3 similar decisions are needed to determine whether a study is included or excluded. Any disagreements between individual judgments will be discussed and resolved together. The selected studies were assessed to extract the following information: first author's name and publication year, study design, study characteristics (country, study center, and study period), definition of variables, participant demographics and baseline characteristics (sample size and age), primary and secondary outcomes, and confounding variables. The primary outcome assesses changes in brain perfusion post-rhythm control. If applicable, the secondary outcome examines neurocognitive function. A significance level of $p < .05$ was applied.

2.4 | Quality assessment

Included studies were assessed by two authors, RY and J, independently through critical appraisal considering the risk of potential for

selection bias, information bias, measurement bias, or confounding using the National Institutes of Health Quality Assessment Tool for cohort and cross-sectional studies.[22] Any discrepancies in the assigned scores were addressed through discussion, and the final quality assessment score for each study was obtained by averaging the scores from each reviewer.

3 | RESULTS

3.1 | Study selection

We found 691 studies in the initial database search. After removing duplicates and screening potentially eligible studies from each database and registry, 10 studies[11,19,21,23–29] met our criteria and were included. In the final selection step, several studies were excluded.[30–34] Among them, one study focused on comparing brain activities instead of assessing brain perfusion before and after rhythm control.[30] Another study specifically investigated brain saturation as a monitoring parameter during totally thoracoscopic ablation surgeries.[31] Additionally, three studies solely compared neurocognitive function.[32–34] The PRISMA flow diagram in Figure 1 illustrates the selection process. The selected studies underwent bias risk assessment, and the results are detailed in Table S1. Two studies were rated as "good," while eight studies received a rating of "fair" in the assessment of quality.

3.2 | Study characteristics

We included ten studies in our analysis, with a total of 436 participants (Table 1). Among these studies, seven were cohort studies, and three were cross-sectional studies. They were published between 1989 and 2023 and conducted in various countries, including Russia,[23] Croatia,[24] Japan,[11,25] Iceland,[19] Denmark,[26] Poland,[27] Belgium,[28] Germany,[29] and Italy.[21]

Eight of the studies[11,21,23–26,28,29] involved patients with paroxysmal or persistent AF lasting less than 1 year, while the other two studies[19,27] diagnosed AF using only electrocardiography (ECG). In terms of rhythm control, nine studies utilized mechanical strategies, and one study[27] employed a pharmacological approach (amiodarone). Among the mechanical strategies, six used electrical cardioversion (ECV),[19,21,24,26,28,29] and the other three employed radiofrequency ablation (RFA) or cryoballoon techniques.[11,23,25] Brain perfusion was reported as the measure of CBF in seven studies,[11,19,23–27] cerebral tissue oxygen saturation (SctO2) in two studies,[28,29] and tissue hemoglobin index (THI) in one study.[21] Table S2 provides details on the definitions used in these studies.

3.3 | Outcomes

The results of brain perfusion before and after rhythm control, as well as neurocognitive measurements after sinus restoration, are presented in Tables 2 and 3, respectively. Studies included measured regional CBF (rCBF), total CBF, SctO2, and THI. Eight studies reported a statistically significant improvement in brain perfusion following the restoration of sinus rhythm.[11,19,23,24,26–29] One study indicated significant improvement in only one brain region, while overall improvement was deemed insignificant.[25]

Among the studies reviewed, only two reported on the percentage of perfusion improvement.[23,28] Efimova et al[23] demonstrated an average increase in rCBF of 11.5% ($p = .01$) in the right inferior frontal, 5% ($p = .007$) in the left superior frontal, and 6% ($p = .005$) in the left temporal cortex compared to baseline values. Genbrugge et al[28] observed an increase in SctO2 values, with a maximum elevation of 6% above baseline SctO2 values ($p < .001$) following restoration of sinus rhythm. Conversely, no immediate change in SctO2 was noted after cardioversion when sinus rhythm was not restored, with a maximum observed increase of 2% ($p = .287$).[28] Additionally, SctO2 values 4–6 weeks postunsuccessful cardioversion were even lower compared to baseline ($p = .041$).[28]

In the cohort studies, follow-up periods varied in the short term from immediately after rhythm control to <3 months and in the midterm to <6 months. Both short-term and mid-term follow-up periods showed significant increases in brain perfusion after sinus rhythm restoration.[11,19,23–26,28] One study reported an increase in CBF at 1 month and continued to increase significantly at 6-month follow-up.[11] One study reported a significant increase in SctO2 immediately after successful ECV, but there was no significant difference in the follow-up at weeks 4–6 compared to baseline.[28] Three studies reported AF recurrence during the follow-up period. All three studies indicated no significant change in brain perfusion compared to baseline.[11,24,28]

Neurological testing was conducted in four of the studies to evaluate cognitive deficits or improvement before and after rhythm control in AF.[23–25,28] Two studies reported a positive impact on cognitive function following RFA.[23,25] Both studies demonstrated improvement in the Rey Auditory Verbal Learning Test (AVLT), which is used to assess immediate verbal memory, delayed memory, learning, and attention.

4 | DISCUSSION

This study systematically examined the scientific literature on how rhythm control affects brain perfusion in patients with atrial fibrillation.[14] Research on human cerebral circulation, vital for brain function, grapples with complexities in modeling hemodynamics and oxygenation.[35] Factors such as blood flow velocity distributions, oxygen transport, cerebral autoregulation, vascular compliance, and multiple vascular contributions complicate the task.[35] Two categories of measurement methods, direct and indirect, address this complexity.[14] Direct methods employ contrast agents in techniques such as SPECT, PET, MRI, xenon CT, and arterial spin labeling (ASL) MRI, quantifying CBF, cerebral blood volume, and
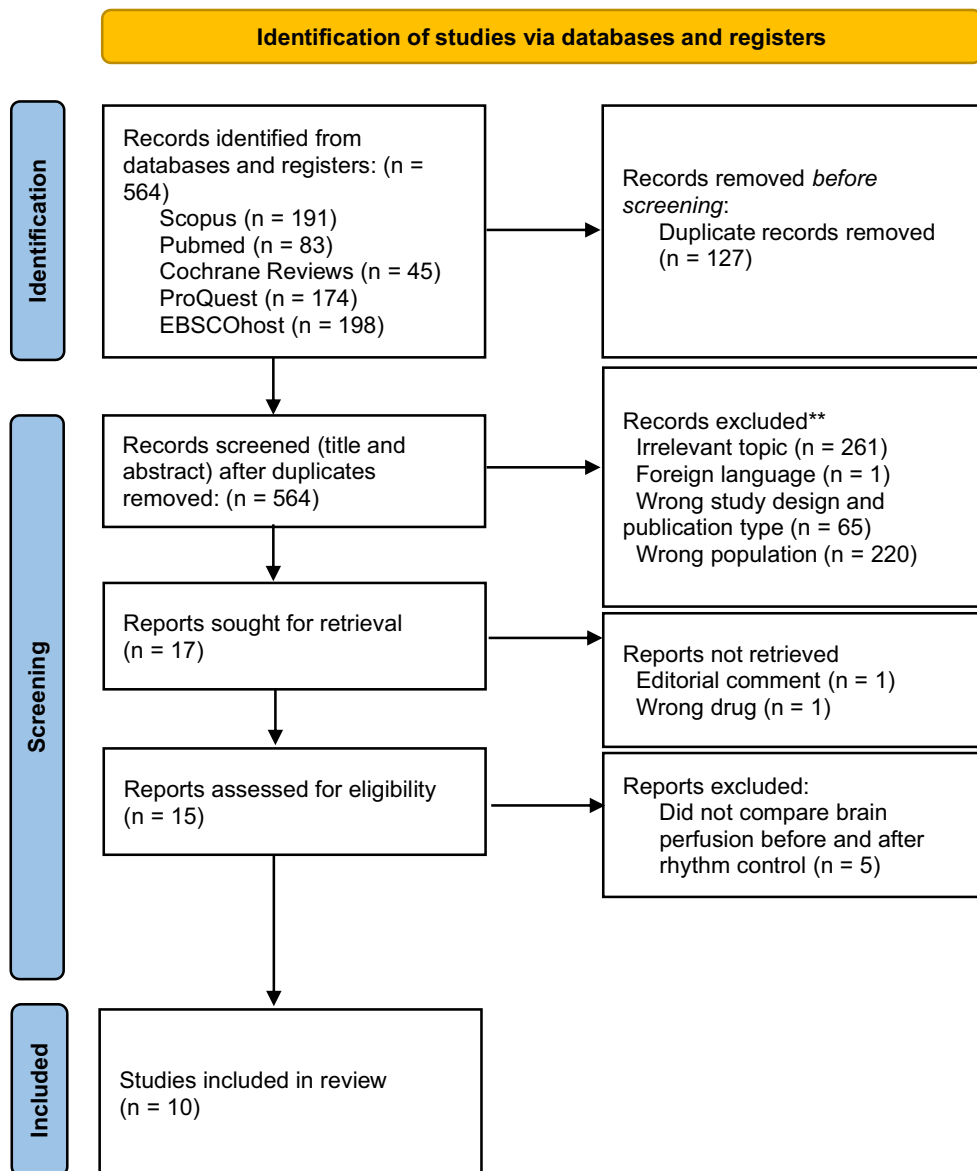
Identification of studies via databases and registers

Identification

Records identified from databases and registers: (n = 564)
Scopus (n = 191)
Pubmed (n = 83)
Cochrane Reviews (n = 45)
ProQuest (n = 174)
EBSCOhost (n = 198)

→ Records removed *before screening*:
Duplicate records removed (n = 127)

Screening

Records screened (title and abstract) after duplicates removed: (n = 564)

→ Records excluded**
Irrelevant topic (n = 261)
Foreign language (n = 1)
Wrong study design and publication type (n = 65)
Wrong population (n = 220)

Reports sought for retrieval (n = 17)

→ Reports not retrieved
Editorial comment (n = 1)
Wrong drug (n = 1)

Reports assessed for eligibility (n = 15)

→ Reports excluded:
Did not compare brain perfusion before and after rhythm control (n = 5)

Included

Studies included in review (n = 10)

FIGURE 1 PRISMA flowchart depicting the detailed steps of study selection.

metabolic rate of oxygen.[14,35] Indirect techniques, including NIRS, transcranial Doppler, and phase-contrast MRI, measure physiological parameters reflecting cerebral perfusion.[14,35] AF significantly impacts perfusion by disrupting the regularity of diastolic and systolic timing, leading to beat-to-beat variability in cardiac output and decreased CBF.[36,37] This impairment in CBF, despite normal stroke volume, may result in cerebral hypoperfusion, particularly as AF progresses.[36] Notably, flow-mediated dilation improves after cardioversion and catheter ablation, indicating some reversibility of arrhythmia-induced dysfunction.[36,38] Our analysis indicates that rhythm control may enhance brain perfusion, supported by 7 studies[11,19,23–27] with direct measurement and 3 studies with indirect measurement.[21,28,29] The indirect methods encompass SctO2 and THI. Previous studies have revealed a positive correlation between SctO2 levels and cerebral perfusion pressure, as well as cognitive function.[29] Meanwhile, THI assesses the concentration

of total hemoglobin in tissues, indicating alterations in local cerebral tissue blood volume, thereby offering an indirect measure of local microvascular perfusion.[21]Of all the studies, the success rates for improving brain perfusion through rhythm control strategies were as follows: ablation, 66.7% (2/3); ECV, 83.3% (5/6); and amiodarone, 100% (1/1).

These findings are attributed to various factors. Initially, restoring sinus rhythm alleviates the hemodynamic decline from AF, boosting brain perfusion. Takahashi et al. further investigated changes in CBF based on heart rhythm during MRI scanning in both AF-SR and SR-SR groups.[11] They found that CBF continued to increase over 6 months following ablation, extending beyond the initial 1-month period if SR is maintained. The sustained elevation in CBF postablation implies that the higher CBF in SR group cannot be solely because of inherent differences between SR and AF rhythms from the baseline.

TABLE 1 Characteristics of studies.

Author, year	Country	Study design	Participants	Age (mean ± SD or median (IQR))	Outcomes	Exclusion criteria	Measure of potential confounding variables
Efimova et al, 2012[23]	Russia	Cohort	AF: 17 Non-AF: 15	AF: 55.3 ± 4.5 Non-AF: 52.5 ± 3.8	rCBF (using brain SPECT, images were divided into 14 symmetrical (right and left) regions of interest), comprehensive neuropsychological testing (the Rey AVLT, digit span forward-backward, token test, digit symbol test, the Bourdon-Wiersma dot cancellation test, TMT-A, TMT-B, the complex figure test (CFT)), and echocardiography	Organic damage of target organs (including myocardial infarction, stroke and silent cerebral infarction, stenosed atherosclerosis of carotid arteries, or chronic renal insufficiency), serious vision and hearing deficiency, psychiatric illnesses (including drug abuse and chronic alcoholism), a history of craniocerebral injury or neuroinfection, and serious concomitant diseases	NR
Kedžo et al, 2023[24]	Croatia	Cohort	AF: 25 Non-AF: 16	AF: 67 ± 8 Non-AF: 66 ± 4	Comparisons of regional brain perfusion measured by ASL MRI between patients with persistent AF and control subjects and within patients with persistent AF, before and 6 weeks after the ECV, changes in blood pressure, heart rate, levels of biomarkers (NT-proBNP, hsTnT, vWF) before and 6 weeks after the ECV, and comparison of cognitive function between patients with persistent AF and control subjects, and within patients with persistent AF, before and 6 weeks after the ECV	Long-standing persistent AF (>1-year duration of ongoing episode), atrial flutter, LVEF <40%, severe valvular disease, history of stroke/transient ischemic attack, intervention on carotid arteries, diagnosis of significant (>70%) stenosis of carotid arteries on imaging or presence of carotid bruit on physical examination, cognitive disorders or dementia, any diagnosed neurologic disease, and any diagnosed psychiatric disorder, also patients with cardiac implantable electronic devices or other contraindications for MRI	Age, gender, height, weight, BMI, SBP, DBP, HR, diagnostic test (hemoglobin, hematocrit, creatinine, eGFR, blood glucose, albumin, total cholesterol, LDL, NT-pro BNP, hs-TnT, vWF, and PROMIS), comorbidities (smoking, HT, DM, and CKD), and medications (anticoagulants, antiplatelets, anti-HT, and statins)
Tatewaki et al, 2023[25]	Japan	Cohort	AF: 8 Non-AF: 7	AF: 63.4 ± 7.3 Non-AF: 63.0 ± 6.9	Cognitive-psychological tests, cardiac function with echocardiography, serum BNP concentrations, rCBF with ASL MRI, and regional cortical thickness with structural MRI	Neuro-psychological disorders, coexisting severe medical conditions or terminal diseases (e.g., stroke, Parkinson's disease, thyroid/parathyroid disease, and cancer) that may influence the results of the imaging and cognitive studies, difficulty in obtaining written informed consent, difficulty in undergoing brain MRI (pacemaker implantation, coronary artery stenting, other metal device implantation, or claustrophobia), difficulty in undergoing cognitive tests (amblyopia, deafness, and orthopedic impairment), and failure to acquire rhythm control through ablation therapy	Age, gender, heart rate, LAD, LVDd, LVDs, EF, LA volume, LA volume index, CO, CI, and serum BNP level

TABLE 1 (Continued)

Author, year	Country	Study design	Participants	Age (mean ± SD or median (IQR))	Outcomes	Exclusion criteria	Measure of potential confounding variables
Gardarsdottir et al, 2019[19]	Iceland	Cohort	Overall: 27	Overall: 64.4	Perfusion and CBF (ASL whole brain, ASL gray matter, and total CBF) first and second visits and change between visits	Those with a pacemaker, implantable cardioverter, or other contraindications for MRI, severe claustrophobia, recurrence of AF after being cardioverted to sinus rhythm during the observation period, spontaneous return to SR before the cardioversion	Age, height, weight, BMI, SBP, DBP, baseline HR, smoking status, HT, lipid disorder, coronary heart disease, history of PCI/CABG, valve disease, cardiac surgery, reduced cardiac contractility, clinical HF, stroke/cerebral infarct or embolus, and medications (anti-HT, anticoagulants, aspirin, lipid lowering, antidiabetes, and antiarrhythmia)
Takahashi et al, 2022[11]	Japan	Cohort	AF undergoing RFA: 57; AF undergoing only medical therapy: 11	AF undergoing RFA: 64 ± 11; AF undergoing only medical therapy: 67 ± 5	The adjusted means of change of CBF, brain perfusion, total brain volume, and bilateral hippocampal volume from baseline to the 6-month follow-up between the study and control groups	Contraindications for MRI (which included patients with implantable electric devices) and history of carotid artery disease	Age, gender, BMI, AF type (nonparoxysmal and paroxysmal), presence of HF, DM and prior thromboembolism, CHA2DS2-VASc score, current and former smoking, medications (oral anticoagulation, lipid-lowering agents, and renin-angiotensin-aldosterone inhibitors), HR, eGFR, BNP, LDL and HDL cholesterol, LAD, and LVEF
Petersen, et al, 1989[26]	Denmark	Cohort	AF: 9	AF: 61 (24-63)	CBF, echocardiography, CO, electrocardiography, SBP, and HR before and after ECV to SR	Systemic hypertension, congestive heart failure, chronic renal failure, and history of head injury and cerebrovascular disease	NR
Porebska, et al, 2007[27]	Poland	Cross-sectional	AF: 30; Non-AF: 35	AF: 72 (54-87); Non-AF: 57 (39-79)	Blood flow through the MCAs in AF and healthy control, during an AF attack and after cardioversion (mean flow velocity in the MCA)	History of stroke, signs of recent cerebral ischemia, CT abnormalities resulting from previous or recent cerebrovascular accident, and AF patients taking antiarrhythmic drug other than amiodarone	Age, gender, arterial HT, DM, ischemic heart disease, dyslipidemia, baseline SBP and DBP, and antiarrhythmic drugs (amiodarone)
Genbrugge, 2020[28]	Belgium	Cohort	AF successful ECV: 50; AF Unsuccessful ECV: 10; Non-AF: 20	AF successful ECV: 67 [60-73]; AF unsuccessful ECV: 75 [70-83]; Non-AF: 68 [53-81]	SctO2, neuropsychological function (AVLT, MMSE, TMT-A, TMT-B, and symbol coding), and quality of life (physical functioning, social functioning, role limitations (physical and emotional), mental health, vitality, pain, general health, and change in health)	COPD GOLD class III-IV, carotid artery disease or previous cardiopulmonary resuscitation, and brain atrophy	Age, gender, baseline SctO2, SpO2, MAP, HR, paroxysmal/persistent AF, AF history, sedating during ECV, comorbidities (cerebrovascular accident/transient ischemic attack, COPD GOLD class I-II, DM, arterial HT, structural heart disease, ischemic heart disease, pacemaker/cardiac resynchronization therapy, acute myocardial infarction), and baseline medication (antiarrhythmia, anti-HT, statins, diuretics, statins, LMWH, oral anticoagulants, and aspirin)

TABLE 1 (Continued)

Author, year	Country	Study design	Participants	Age (mean ± SD or median (IQR))	Outcomes	Exclusion criteria	Measure of potential confounding variables
Wutzler, et al, 2014[29]	Germany	Cross-sectional	Overall: 30 AF successful CV: 20 AF unsuccessful CV: 10	Overall: 66.5 ± 9.5 AF successful CV: 67.7 ± 19.2 AF unsuccessful CV: 64.2 ± 7.7	SctO2, changes of ABP, HR, and SaO2	First-diagnosed, long-standing persistent or permanent AF, left atrial thrombus, acute myocardial infarction, acute or decompensated chronic HF, stroke, brain injury, or other severe comorbidity	Age, gender, BMI, paroxysmal AF, persistent AF, hypertension, coronary artery disease, structural heart disease, DM, peripheral artery disease, LVEF, LAD, baseline SctO2 right and left, baseline SaO2, baseline MAP, baseline HR, baseline medication (antiarrhythmic, anti-HT, diuretics, statins, anticoagulants, and aspirin), and anesthetics during cardioversion
Saglietto, et al, 2021[21]	Italy	Cross-sectional	Overall: 53	AF: 69 ± 9 Non-AF: 69 ± 10	Inter-beat THI and ABP variability before and after ECV	First-diagnosed, long-standing persistent (>1-year duration of the ongoing episode), and permanent AF; AF in the presence of precipitating factors (sepsis, acute myocardial ischemia, and untreated dysthyroidism); severe comorbidities (e.g., hepatic injury and renal failure); hemodynamic instability [SBP <90mmHg, altered consciousness, or reduced peripheral perfusion documented by an increased arterial blood lactate (>2mmol/L)]; and electrolyte abnormalities	Age, gender, BMI, HT, DM, previous stroke/transient ischemic attack, supra-aortic trunk stenosis, EHRA class, HF, coronary artery disease, CHAD2DS2-VASc score, HAS-BLED score, cardiac implantable device, echocardiographic parameters (LVEF, indexed LAV, and end-diastolic LVD), and medications

Abbreviations: ABP, arterial blood pressure; AF, atrial fibrillation; ASL, arterial spin labeling; BMI, body mass index; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CI, cardiac index; CKD, chronic kidney disease; CO, cardiac output; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; ECV, electrical cardioversion; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, heart rate; hsTnt, high-sensitivity cardiac troponin; HT, hypertension; LAD, left atrial dimension; LA, left atrium; LAV, left atrial volume; LDL, low-density lipoprotein; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MCA, middle cerebral artery; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NR, not reported; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; PROMIS, Patient-Reported Outcomes Measurement Information System; RFA, radiofrequency ablation; rCBF, regional cerebral blood flow; SaO2, arterial oxygen saturation; SBP, systolic blood pressure; SctO2, cerebral tissue oxygen saturation; SPECT, single-photon emission computed tomography; SpO2, peripheral oxygen saturation; SR: sinus rhythm; THI, tissue hemoglobin index; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; vWF, von Willebrand factor.

TABLE 2 Main outcomes.

Study	Study design	Rhythm control	Brain perfusion index	Follow-up period	Before-after (p-value)	Conclusion
Cerebral blood flow (CBF)						
Efimova et al, 2012[23]	Cohort	RFA followed by pacemaker implantation	rCBF	3 months	a. Right interior frontal: .01 b. Left superior frontal: .007 c. Left temporal cortex: .005	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Kedžo et al, 2023[24]	Cohort	Electrical cardioversion	rCBF	6 weeks	a. Successful: <.05, except in the left frontal white matter region (.05) b. Unsuccessful: >.05 in all region	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Tatewaki et al, 2023[25]	Cohort	RFA or cryo-balloon	a. Whole cerebral gray matter CBF ratio b. rCBF	6 months	a. .77 b. .013	Brain perfusion is not significantly improved in the restoration of sinus rhythm group, except in the left posterior cingulate gyrus
Gardarsdottir et al, 2019[19]	Cohort	Electrical cardioversion	a. Total CBF b. Whole brain CBF c. Whole cerebral gray matter CBF ratio	10 weeks	a. <.05 b. <.001 c. <.001	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Takahashi et al, 2022[11]	Cohort	Catheter ablation	CBF in: a. Paroxysmal AF at baseline with no recurrence b. Nonparoxysmal AF with no recurrence c. Recurrence of AF after ablation	6 months	a. .78 b. <.0001 c. .15	Brain perfusion is significantly improved after restoration of sinus rhythm in the nonparoxysmal AF group
Petersen et al, 1989[26]	Cohort	Electrical cardioversion	CBF (corrected with level of pCO2)	1 and 30 days	.018	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Porebska et al, 2007[27]	Cross-sectional	Amiodaron	Mean flow velocity of right and left medial cerebral arteries (MCAs)	NA	a. Right MCA: .008 b. Left MCA: .004	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Cerebral saturation						

Genbrugge et al, 2020[28]	Cohort	Electrical cardioversion	Regional SctO2	a. After ECV
				b. 4–6 weeks
					a. Successful: <.001
					  Unsuccessful: .481
					b. Successful: .077
					  Unsuccessful: .041
						Brain perfusion is significantly improved in the restoration of sinus rhythm group after ECV

Wutzler et al, 2014[29]	Cross-sectional	Electrical cardioversion	a. Right ΔSctO2* b. Left ΔSctO2*	NA	a. .001 b. <.001	Brain perfusion is significantly improved in the restoration of sinus rhythm group
Others						
Saglietto et al, 2021[21]	Cross-sectional	Electrical cardioversion	Tissue hemoglobin index (THI)	NA	.266	Brain perfusion is not significantly improved in the restoration of sinus rhythm group

Abbreviations: AF, atrial fibrillation; CBF, cerebral blood flow; ECV, electrical cardioversion; MCA, medial cerebral artery; RFA, radiofrequency ablation; rCBF, regional cerebral blood flow; SctO2, cerebral tissue oxygen saturation.

*Delta values were calculated from baseline and post-ECV values.

TABLE 3 Secondary outcomes.

Study	Participants/total AF sample	Neurocognitive measurement index	Summary of findings
Efimova et al, 2012[23]	17/17	AVLT, digit span forward-backward, token test, digit symbol test, DCT, TMT, and CFT	Radiofrequency ablation followed by pacemaker implantation had a positive effect on cognitive function in all patients ($p < .01$ in all indexes, except DCT < 0.05; TMT-B < 0.05; and 30 min CFT < 0.05).
Kedzo et al, 2023[24]	Successful ECV = 15/25	Patient-Reported Outcomes Information System (PROMIS) Cognitive Function index	No change in cognitive function in patients without arrhythmia recurrence after ECV ($p = .46$).
Tatewaki et al, 2023[25]	8/8	MMSE, WAIS, TMT, and AVLT recognition (total recall, learning, and forgetting)	Improvements in a broad spectrum of cognitive domains (MMSE ($p = .023$), WAIS digit symbol ($p = .008$), and recognition AVLT total recall ($p = .023$)).
Genbrugge et al, 2020[28]	Successful ECV = 19/69 Unsuccessful ECV = 4/69	AVLT, MMSE, TMT, and symbol codding	No difference was observed in extensive neuropsychological functioning before and after ECV, independently if ECV was successful or not.

Abbreviations: AVLT, Rey Auditory Verbal Learning Test; CFT, complex figure test; DCT, Bourdon-Wiersma dot cancellation test; ECV, electrical cardioversion; MMSE, Mini-Mental State Examination; TMT, trail making test; WAIS, Wechsler Adult Intelligence Scale.

In three studies comparing CBF between AF and SR groups at baseline,[23,24,27] only one study demonstrated higher values in the SR group.[23] The absence of baseline differences in brain perfusion between AF patients and control subjects suggests that, in the long term, other cardiovascular comorbidities such as hypertension may also play a role.[24,39] Factors such as advanced age, the use of antihypertensive medications, high cholesterol levels, and active smoking were identified as significant confounders for the reduction in CBF.[40] Moreover, comparing the SR group with paroxysmal AF only may yield no difference, as individuals with paroxysmal AF often exhibit more efficient heart and circulatory system function than those with chronic AF.[27] Although disturbances in cerebral circulation occur during paroxysmal AF, they typically do not lead to clinical signs of brain ischemia.[27] This is supported by study findings indicating a significant increase in CBF (13.7%) in patients with nonparoxysmal AF who were free from atrial tachyarrhythmias after ablation, while insignificant changes were observed in the paroxysmal group.[11]

Another explanation for how rhythm control could impact brain perfusion is through the enhancement of cardiac outputs (COs). Efimova et al[23] observed a 15% improvement in CO ($p = .0015$) and a 6% increase in average left ventricular ejection fraction at 3 months after ablation and pacing. This aligns with Genbrugge et al's[28] findings, suggesting that a sudden increase in CO following successful ECV is positively associated with SctO2. This could be attributed to atrial and ventricular resynchronization, restoring atrial booster pump function and preventing atrioventricular valve regurgitation.[28] The return of SctO2 to baseline values at 4–6 weeks may result from a decreased CO or a delayed activation of cerebral autoregulation.[28] In the latter case, the cerebral autoregulation mechanisms were assumed to be transiently stunned by the sudden increase in CO after successful ECV.[28]

There are various mechanisms explaining improved CBF following different rhythm control strategies. Catheter ablation, considered the gold standard, not only maintains SR but also denervates the epicardial ganglionated plexi through direct thermal injury.[11] The effects of catheter ablation on endothelial function or inflammation may further impact brain perfusion by modulating autoregulation of cerebral arteries and arterioles.[25,41] In contrast, Kedzo's examination of factors related to this pathophysiology found no decrease in vWF values after restoring sinus rhythm, suggesting that endothelial dysfunction may not be the primary mediator of cerebral perfusion improvement.[24] On the other hand, cardioversion, both electrical and pharmacological, significantly reduces hypoperfusive and hyperperfusive/hypertensive microcirculatory events in cerebral circulation.[21,24] Therefore, the enhancement of brain perfusion in sinus rhythm can be attributed to the restoration of contractile atrial function, improved diastolic filling of the ventricles, and reduced heart rate variability.[21,24]

Two studies found no significant improvement in brain perfusion with rhythm control, but these results do not contradict the other eight studies. Tatewaki et al[25] observed improved cognitive domains and regional CBF in the left retrosplenial cortex following AF ablation. This cortex plays a crucial role in cognitive functions affected in early Alzheimer's disease.[25] The authors propose that restoring sinus rhythm corrects autonomic hyperactivity, enhancing vascular reactivity and blood flow in the posterior cingulate cortex, a region vulnerable to autoregulation dysfunction.[25] Secondly, although Saglietto et al[21] found no significant mean THI differences pre- and post-ECV, sinus rhythm restoration significantly reduced extreme single-beat hemodynamic events in cerebral microcirculation. Interbeat THI variability, reflecting perfusion changes in cerebral microcirculation, significantly varied after cardioversion, emphasizing the

greater impact of AF-induced disturbances on distal cerebral circulation compared to the systemic district.[21]

4.1 | Secondary outcomes: discussion

Chronic brain hypoperfusion is suggested as a potential mechanism linking AF to cognitive decline.[19] Three contributors to this decline are silent cerebral ischemia, inflammation, and altered cerebral blood flow.[37] In our analysis of four studies on rhythm control's impact on cognitive function or neuropsychological functioning in AF, only two showed a positive effect.[23,25]

Efimova et al and Tatewaki et al[23,25] observed improvements across various cognitive domains following AF ablation. This finding is supported by Jin's study, which demonstrated a significant enhancement in cognitive function (assessed using the Montreal Cognitive Assessment) in an AF ablation group at 3 months and 1-year postablation.[42] Another prospective study involving 74 Japanese patients who underwent AF ablation reported significant improvements in scores for MMSE, immediate recall, delayed recall, constructional visuospatial ability, and Trail Making Test (TMT) 6 months after ablation therapy.[34] RFA of the atrioventricular node followed by pacemaker implantation has been shown to increase left ventricular ejection fraction, systolic function, and cardiac outputs.[23] Tatewaki notes that the AF group initially showed lower cognitive function than normal controls, but lifestyle factors were not adjusted for.[25] Shared risk factors for AF and cognitive impairment include aging, smoking, hypertension, diabetes, sleep apnea, physical inactivity, vascular disease, inflammation, and heart failure.[43] The authors speculate that AF-related adverse factors and CO may contribute to cognitive recovery after ablation therapy.[25]

The two other studies utilizing ECV reveal insignificant differences in cognitive functions post-successful ECV.[24,28] However, the interval between the pre- and post-cardioversion MRI examinations was only a few weeks. This time frame is likely insufficient to detect differences, as improvements have been observed over a more extended period.[44] A prior study recommends a minimum of 3 months for assessing long-term neuropsychological functioning.[45]

4.2 | Limitations

This study represents the inaugural systematic review concentrating on the correlation between rhythm control in atrial fibrillation and cerebral perfusion. We tried to synthesize the most significant findings from existing studies to date. The investigation of whether sustaining SR can potentially defer the onset of brain atrophy or cognitive decline warrants further exploration, despite the intriguing results obtained in this study. However, it is crucial to recognize the study's limitations. The inclusion of studies with a limited sample size and diverse types of AF may introduce selection bias. Additionally, variations in rhythm control strategies

and approaches to measuring brain perfusion exist across studies. While we attempted to mitigate this issue by clearly defining the terms in each study for the reader's consideration, addressing these limitations remains essential. The recommendation for future study is for more targeted and specific research focusing on the specific type of AF, brain perfusion parameters, and more direct measurement methods.

5 | CONCLUSION

The findings from this study align with the understanding that addressing the hemodynamic decline induced by AF can positively impact brain perfusion. This systematic review suggests that successful rhythm control in AF holds promise as a therapeutic intervention for enhancing brain perfusion and potentially mitigating cognitive decline. However, to establish this link conclusively and inform clinical practice, it is imperative to conduct larger-scale prospective studies and randomized trials. These endeavors will contribute valuable insights into the nuanced interplay between rhythm control, cerebral perfusion, and cognitive function, paving the way for more targeted and effective therapeutic approaches in the management of AF-associated cognitive impairment.

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REFERENCES
1. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century, novel methods and new insights. Circ Res. 2020;127(1):4–20. Available from: /pmc/articles/PMC7577553/
2. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. Fifty-year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the community. Lancet (London,

England) 2015;386(9989):154–62. Available from: /pmc/articles/PMC4553037/

3. Yang SY, Huang M, Wang AL, Ge G, Ma M, Zhi H, et al. Atrial fibrillation burden and the risk of stroke: a systematic review and dose-response meta-analysis. World J Clin Cases. 2022;10(3):939–53. Available from: /pmc/articles/PMC8790433/

4. Poggesi A, Inzitari D, Pantoni L. Atrial fibrillation and cognition: epidemiological data and possible mechanisms. Stroke 2015;46(11):3316–21. Available from: https://pubmed.ncbi.nlm.nih.gov/26396028/

5. Rivard L, Friberg L, Conen D, Healey JS, Berge T, Boriani G, et al. Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration. Circulation. 2022;145(5):392–409. Available from: https://www.ahajournals.org/doi/abs/ https://doi.org/10.1161/CIRCULATIONAHA.121.055018

6. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med. 2013;158(5 PART 1):338–46.

7. Liu DS, Chen J, Jian WM, Zhang GR, Liu ZR. The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies. J Geriatr Cardiol. 2019;16(3):302–10.

8. Islam MM, Poly TN, Walther BA, Yang HC, Wu CC, Lin MC, et al. Association between atrial fibrillation and dementia: a meta-analysis. Front Aging Neurosci. 2019;11:305.

9. Saglietto A, Matta M, Gaita F, Jacobs V, Bunch TJ, Anselmino M. Stroke-independent contribution of atrial fibrillation to dementia: a meta-analysis. Open Heart. 2019;6(1):e000984.

10. Kwok CS, Loke YK, Hale R, Potter JF, Myint PK. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. Neurology. 2011;76(10):914–22.

11. Takahashi Y, Yamamoto T, Oyama J, Sugihara G, Shirai Y, Tao S, et al. Increase in cerebral blood flow after catheter ablation of atrial fibrillation. JACC Clin Electrophysiol. 2022;8(11):1369–77.

12. Hunter TJ, Joseph JJ, Anazodo U, Kharche SR, McIntyre CW, Goldman D. Atrial fibrillation and anterior cerebral artery absence reduce cerebral perfusion: a De novo hemodynamic model. Appl Sci 2022, 12, 1750. Available from: https://www.mdpi.com/2076-3417/12/3/1750/htm

13. Krainik A, Villien M, Troprès I, Attyé A, Lamalle L, Bouvier J, et al. Functional imaging of cerebral perfusion. Diagn Interv Imaging. 2013;94(12):1259–78.

14. Moradi S, Ferdinando H, Zienkiewicz A, Särestöniemi M, Myllylä T, Moradi S, et al. Measurement of cerebral circulation in human. In: cerebral circulation - updates on models, diagnostics and treatments of related diseases. Italy: IntechOpen; 2022. Available from: https://www.intechopen.com/chapters/80543

15. Junejo RT, Lip GYH, Fisher JP. Cerebrovascular dysfunction in atrial fibrillation. Front Physiol. 2020;11:1066. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33013456

16. Xing CY, Tarumi T, Liu J, Zhang Y, Turner M, Riley J, et al. Distribution of cardiac output to the brain across the adult lifespan. J Cereb Blood Flow Metab. 2017;37(8):2848. Available from: /pmc/articles/PMC5536794/

17. Alpert JS, Petersen P, Godtfredsen J. Atrial fibrillation: natural history, complications, and management. Annu Rev Med. 1988;39:41–52. Available from: https://pubmed.ncbi.nlm.nih.gov/3285783/

18. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. Anesthesiology. 2015;123(5):1198–208.

19. Gardarsdottir M, Sigurdsson S, Aspelund T, Gardarsdottir VA, Forsberg L, Gudnason V, et al. Improved brain perfusion after electrical cardioversion of atrial fibrillation. Europace. 2019;22(4):530–7.

20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Available from:https://pubmed.ncbi.nlm.nih.gov/33782057/

21. Saglietto A, Scarsoglio S, Canova D, Roatta S, Gianotto N, Piccotti A, et al. Increased beat-To-beat variability of cerebral microcirculatory perfusion during atrial fibrillation: a near-infrared spectroscopy study. Europace. 2021;23(8):1219–26.

22. National Heart, Lung and BI. Study quality assessment tools. 2017. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

23. Efimova I, Efimova N, Chernov V, Popov S, Lishmanov Y. Ablation and pacing: improving brain perfusion and cognitive function in patients with atrial fibrillation and uncontrolled ventricular rates. Pacing Clin Electrophysiol. 2012;35(3):320–6.

24. Kedžo J, Lovrić Kojundžić S, Marinović Guić M, Tandara L, Brešković T, Jurišić Z. Association of electrical cardioversion with brain perfusion and cognitive function in patients with atrial fibrillation. Life (Basel, Switzerland). 2023;13(4):935. Available from: http://www.ncbi.nlm.nih.gov/pubmed/37109463

25. Tatewaki Y, Mutoh T, Sato H, Kobayashi A, Totsune T, Thyreau B, et al. Impact of catheter ablation on brain microstructure and blood flow alterations for cognitive improvements in patients with atrial fibrillation: a pilot longitudinal study. J Clin Med 2022;11(15):4346. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85136468918&doi=10.3390%2Fjcm11154346&partnerID=40&md5=6fe778a14302ad867841ef5e12cc1be4

26. Petersen P, Kastrup J, Videbaek R, Boysen G. Cerebral blood flow before and after cardioversion of atrial fibrillation. J Cereb Blood Flow Metab 1989;9(3):422–5. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0024307515&doi=10.1038%2Fjcbfm.1989.62&partnerID=40&md5=fb608889f90f15026a9ea9af86982cd9

27. Porebska A, Nowacki P, Safranow K, Drechsler H. Nonembolic, hemodynamic blood flow disturbances in the middle cerebral arteries in patients with paroxysmal atrial fibrillation without significant carotid stenosis. Clin Neurol Neurosurg. 2007;109(9):753–7.

28. Genbrugge C, Jorissen E, Eertmans W, Jans F, Boer W, Dens J, de Deyne C Increase in regional cerebral saturation after elective electrical cardioversion of atrial fibrillation is only transient and without beneficial effects on neuropsychological functioning: cerebral saturation during electrical cardioversion. J Clin Monit Comput 2021;35(1):165–73. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85077554894&doi=10.1007%2Fs10877-020-00458-2&partnerID=40&md5=3a5d2afe69bdd9442f4109ac1a96621f

29. Wutzler A, Nee J, Boldt L-H, Kühnle Y, Gräser S, Schröder T, et al. Improvement of cerebral oxygen saturation after successful electrical cardioversion of atrial fibrillation. Europace 2014;16(2):189–94. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-84893210306&doi=10.1093%2Feuropace%2Feut246&partnerID=40&md5=2e51336a27f4f384f47ac021d05a975e

30. Akiomi Y, Soichi K, Takashi K, Yasuhiro I, Tomofumi M, Shinya Y, et al. Impaired brain activity in patients with persistent atrial fibrillation assessed by near-infrared spectroscopy and its changes after catheter ablation. Sci Rep. 2022;12(1):7866. Available from: https://www.proquest.com/scholarly-journals/impaired-brain-activity-patients-with-persistent/docview/2663154762/se-2

31. Li G, Yang L, Sun Y, Shen S. Cerebral oxygen desaturation in patients with totally thoracoscopic ablation for atrial fibrillation: a prospective observational study. Medicine. 2020;99(17):e19599.

32. Alosco ML, Spitznagel MB, Sweet LH, Josephson R, Hughes J, Gunstad J. Atrial fibrillation exacerbates cognitive dysfunction and cerebral perfusion in heart failure. Pacing Clin Electrophysiol. 2015;38(2):178–86. Available from:. https://pubmed.ncbi.nlm.nih.gov/25492027/

33. Zhang J, Shi-Jun X, Du X, Jiang C, Yi-Wei L, Yu-Feng W, et al. Incidence and risk factors of post-operative cognitive decline after ablation for atrial fibrillation. BMC Cardiovasc Disord 2021;21:1–12. Available from: https://www.proquest.com/scholarly-journals/incidence-risk-factors-post-operative-cognitive/docview/2552813248/se-2

34. Kato N, Muraga K, Hirata Y, Shindo A, Matsuura K, Ii Y, et al. Brain magnetic resonance imaging and cognitive alterations after ablation in patients with atrial fibrillation. Sci Rep 2021;11(1):18995. Available from: https://www.proquest.com/scholarly-journals/brain-magnetic-resonance-imaging-cognitive/docview/2575651277/se-2

35. Fantini S. Dynamic model for the tissue concentration and oxygen saturation of hemoglobin in relation to blood volume, flow velocity, and oxygen consumption: implications for functional neuroimaging and coherent hemodynamics spectroscopy (CHS). NeuroImage. 2014;85(1):202–21.

36. Zenger B, Rizzi S, Steinberg BA, Ranjan R, Bunch TJ. This is your brain, and this is your brain on atrial fibrillation: the roles of cardiac malperfusion events and vascular dysfunction in cognitive impairment. Arrhythmia Electrophysiol Rev. 2023;12:e01.

37. Kalantarian S, Ruskin JN. Atrial fibrillation and cognitive decline: phenomenon or epiphenomenon? Cardiol Clin. 2016;34(2):279–85.

38. Skalidis EI, Zacharis EA, Tsetis DK, Pagonidis K, Chlouverakis G, Yarmenitis S, et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. Am J Cardiol 2007;99(9):1258–62. Available from: https://pubmed.ncbi.nlm.nih.gov/17478154/

39. van Dalen JW, Mutsaerts HJMM, Petr J, Caan MWA, van Charante EPM, MacIntosh BJ, et al. Longitudinal relation between blood pressure, antihypertensive use and cerebral blood flow, using arterial spin labelling MRI. J Cereb Blood Flow Metab 2021;41(7):1756–66. Available from: https://pubmed.ncbi.nlm.nih.gov/33325767/

40. Wolters FJ, Zonneveld HI, Hofman A, Van Der Lugt A, Koudstaal PJ, Vernooij MW, et al. Cerebral perfusion and the risk of dementia: a population-based study. Circulation 2017;136(8):719–28. Available from: https://pubmed.ncbi.nlm.nih.gov/28588075/71

41. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res. 2014;114(9):1500–15. Available from: https://pubmed.ncbi.nlm.nih.gov/24763467/

42. Jin MN, Kim TH, Kang KW, Yu HT, Uhm JS, Joung B, Lee MH, Kim E, Pak HN Atrial fibrillation catheter ablation improves 1-year follow-up cognitive function, especially in patients with impaired cognitive function. Circ Arrhythm Electrophysiol 2019;12(7):e007197. Available from: https://pubmed.ncbi.nlm.nih.gov/31442075/

43. Dagres N, Chao TF, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? Europace 2018;20(9):1399–400. Available from: https://pubmed.ncbi.nlm.nih.gov/29562326/

44. Park H, Hildreth A, Thomson R, O'Connell J. Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study. Age Ageing. 2007;36(2):157–63. Available from: https://pubmed.ncbi.nlm.nih.gov/17259637/

45. Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, et al. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. Stroke. 2013;44(4):1020–5. Available from: https://pubmed.ncbi.nlm.nih.gov/23444303/

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