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Silent cerebral ischemic lesions in ablation-naïve patients with non-valvular atrial fibrillation: Does the pulmonary vein anatomy matter?

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Abstract

Background: *Silent cerebral ischemic lesions (SCILs) detected by magnetic resonance imaging (MRI) can precede symptomatic stroke, the risk of which is increased five-fold in atrial fibrillation (AF) patients. In our study, we aimed to evaluate the initial incidence of SCILs in the population of patients referred for ablation due to symptomatic AF and to identify possible risk factors.*

Methods: *A total of 110 patients, with a mean age (SD) of 59.9 (9.4) years, referred for ablation, were included in the study. In all patients, MRI was performed before the procedure to evaluate the incidence of SCILs in the ablation-naïve patients.*

Results: *MRI revealed preexisting SCIL in 81/110 patients (73.6%). Notably, SCILs were found in all patients with CHA_2DS_2-VASc score ≥ 4. In univariable analysis, age ($p < 0.001$), CHA_2DS_2-VASc score ($p = 0.001$), hypertension ($p = 0.01$), and anticoagulation duration ($p = 0.023$) were identified as significant risk factors for SCILs, while the presence of anatomical variants of left-sided common pulmonary veins trunk (LCPV) had negative prognostic value ($p = 0.026$). Multivariable logistic regression analysis identified age ($p < 0.001$) as the risk factor of preexisting SCILs, whereas the presence of LCPV trunk was associated with significantly lower ($p = 0.005$) SCILs incidence.*

Conclusions: *Silent cerebral ischemic lesions detected in MRI are frequent in the population of patients with non-valvular AF. The incidence of SCILs is higher in patients with long history of arrhythmia and higher CHA_2DS_2-VASc score. The relationship between the anatomy of pulmonary veins and the incidence of SCILs needs further investigation.* (Cardiol J 2025; 32, 1: 35–42)

Keywords: atrial fibrillation, silent cerebral infarcts, silent stroke

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Introduction

Atrial fibrillation (AF) is associated with an up to five-fold higher risk of symptomatic stroke [1, 2], mainly due to the loss of mechanical function of the atria. Symptomatic stroke can be considered as a visible tip of the iceberg, with much more frequent silent cerebral ischemic lesions (SCILs), detected by magnetic resonance imaging (MRI), hidden below the water [3]. The clinical significance of this phenomenon is being discussed; however, there are data linking silent cerebral lesions with dementia and gradual cognitive decline [4–7]. The clear association between atrial fibrillation and cognitive dysfunction lead to the expert consensus on best practice for the prevention of cognitive decline in the AF population [8]. The known risk factors for thromboembolic complications in the AF population include age, sex, prior stroke, and existing comorbidities: congestive heart failure, diabetes, and vascular disease, integrated in the CHA_2DS_2-VASc score calculation [9]. This score, however, is designed to estimate the risk of symptomatic stroke in patients with atrial fibrillation. Less is known regarding the risk factors for asymptomatic cerebral lesions. Several parameters, including body mass index (BMI), CHA_2DS_2-VASc score, AF duration and type, and concomitant vascular disease [10–14], have been postulated so far. However, in a recently published retrospective analysis of 3 prospective studies, Herm et al. identified age as the only significant risk factor of MRI-detected asymptomatic cerebral ischemic lesions [15]. Conversely, with meticulous long-term monitoring, asymptomatic atrial fibrillation can be detected in up to 49% of patients suffering from cryptogenic stroke [16–18]. Moreover, the chance of detection of silent AF increases with the duration of ECG monitoring [19, 20].

Because silent cerebral lesions can precede symptomatic ischemic stroke [21], the identification of potential risk factors for SCILs is of great importance. In our study, we aimed to evaluate the initial incidence of SCILs detected in preprocedural MRI in the population of patients with symptomatic atrial fibrillation referred for pulmonary vein isolation procedure and identify their potential risk factors.

Methods

Study population

A total of 110 consecutive patients (82 males) with a mean [standard deviation (SD)] age of 59.9 (9.4) years, with documented episodes of symptomatic AF, referred for catheter ablation in our center, were included in the study. None of the patients had a history of stroke or transient ischemic attack (TIA), and all patients were neurologically asymptomatic on admission. All patients received oral anticoagulants — vitamin K antagonists or novel oral anticoagulants (NOACs) — for at least 4 weeks prior to hospital admission.

Exclusion criteria involved previous AF ablation, history of stroke/TIA, enlarged (> 50 mm) left atrium (LA), presence of intracardiac thrombus, valvular heart disease, left ventricular (LV) ejection fraction ≤ 40%, severe heart failure (NYHA class IV), thyroid dysfunction, pregnancy, and contraindication to magnetic resonance imaging. Patient characteristics, including the factors potentially related to thromboembolic risk, are presented in Table 1. The study protocol was approved by the institutional review board (approval number KE-0254/292/2012), and written informed consent was signed by all patients.

Magnetic resonance imaging

In all participants, diffusion-weighted MRI (DW-MRI) was performed before the ablation procedure to evaluate the incidence of SCILs in the ablation-naïve patients. DW-MRI (1.5 Tesla Siemens Avanto) was performed using the standard sequences: T1, T2, FLAIR, SWI/DWI, and 3D FLAIR as described before [22–24]. All MRI scans were analyzed by a certified radiologist, who was blinded to the clinical status of the patients.

Statistical analysis

The statistical analysis was carried out with Tibco Statistica 13.3 (StatSoft, Palo Alto, CA, USA). Normal distribution of continuous variables was tested using the Shapiro-Wilk test. Depending on the distribution, the values of the parameters were presented as arithmetic means and their SD or median and interquartile range (IQR). Student's t test was used for independent variables and the Mann-Whitney U-test as an intergroup comparison component. The distributions of discrete variables in groups were compared with Pearson's chi-square test or Fisher's exact test. Additionally, logistic regression models were fitted to identify risk factors associated with the incidence of SCI. A backward elimination models was built, and nonsignificant variables were removed sequentially until only those significant at $p < 0.05$ remained. From these models, adjusted odds ratios (OR) and 95% confidence intervals were derived; corresponding p values were from Wald's test. Goodness

of fit was checked using Hosmer-Lemeshow's test. The error was set at 5% and significance at a p value < 0.05.

Results

Overall incidence and predictive factors of silent cerebral ischemic lesions

The mean age (SD) of patients enrolled in the study was 59.9 (9.4) years, and the majority were males (82; 74.6%). More than 90% of the population suffered from paroxysmal atrial fibrillation (101; 91.8%), and the arrhythmia was diagnosed approximately 3 years before (median [IQR] 36.0 [24.0–48.0] months). The most prevalent comorbidity was arterial hypertension (83; 74.1%), which was followed by diabetes (23; 20.5%). The overall thromboembolic risk of the studied group assessed with the CHA_2DS_2-VASc score was moderate to median (IQR) 1.0 (1.0–3.0). Detailed characteristics, including the factors potentially related to thromboembolic risk, are presented in Table 1.

Comparison of clinical parameters between the study groups

MRI revealed preexisting SCILs (Fig. 1) in 81 out of 110 (73.6%) patients included in the study. The patients were divided into 2 groups depending on the MRI findings:

— SCIL (+) group — including 81 patients with MRI-detected silent cerebral ischemic lesions, of mean (SD) age 63.0 (7.6) years, 22 females (27.2%);

— SCIL (−) group — including 29 patients without MRI-detected silent cerebral ischemic lesions, of mean (SD) age 51.4 (8.6) years, 6 females (20.7%).

The demographic data, comorbidities, essential echocardiographic and laboratory parameters, together with anatomical variants of pulmonary venous drainage, of patients with and without detected cerebral lesions are presented in Table 2. In univariable analysis, CHA_2DS_2-VASc score ($p < 0.001$) together with its co-factors: age ($p < 0.001$) and hypertension ($p = 0.013$), as well as the time from AF diagnosis ($p = 0.030$), were identified as significant predictors for SCILs. Remarkably, SCILs were found in all patients with CHA_2DS_2-VASc score ≥ 4 (Fig. 2). Conversely, the presence of the anatomical variant of left-sided common pulmonary veins trunk (LCPV) had negative prognostic value ($p = 0.031$) for MRI-detected cerebral ischemic lesions.

Multivariable logistic regression analysis

The logistic regression model based on the variables that were different between the SCIL (+) and SCIL (−) groups identified age ($p < 0.001$) as the only significant risk factor of preexisting SCILs, whereas the presence of the anatomical variant of LCPV trunk was associated with significantly lower ($p = 0.005$) incidence of silent ischemic brain lesions (Tab. 3).

Discussion

Overall incidence of SCILs in the AF population

In our study, we have demonstrated a relatively high incidence of silent ischemic brain lesions in the group of patients with non-valvular atrial fibrillation and moderate risk of thromboembolic events, as assessed with the CHA_2DS_2-VASc score. Previously reported incidence rates of pre-ablation occurrence of silent cerebral lesions in AF patients varies from 14.5% reported by Miki et al. [12] up to 92% in the persistent AF subgroup, published by Gaita et al. [10]. Our finding of 73.6% incidence of SCILs is very similar to the recently published data by Wieczorek et al. [14], who reported a 74.3% incidence rate of silent brain lesions in a similar but less populated group of 74 patients referred for AF ablation.

The identified risk factors for SCILs

In multivariable logistic regression analysis, we have identified age as the only risk factor for SCILs in the studied group of patients with symptomatic recurrences of atrial fibrillation, which is not an unusual finding. Age has been reported as a strong risk factor for MRI-detected silent cerebral ischemic lesions in the general population [25, 26]. Longitudinal studies suggest an annual incidence of SCILs of between 2% and 4% [27]. This is an obvious consequence of the aging process itself, as well as the age-dependent increased rate of comorbidities known to be risk factors for thromboembolic events: arterial hypertension, diabetes, and heart failure [9–12]. This is even truer considering the population of AF patients. In the reports published so far [3, 4, 10–14], age was the only common risk factor for the presence of silent cerebral lesions in the AF population, which was additionally confirmed with our observation. We have also observed a strong correlation between the incidence of SCILs and the CHA_2DS_2-VASc score, which is in fact a combination of known

Table 1. Characteristics of the patients*

Parameter	All patients (n = 110)	SCIL (+) (n = 81)	SCIL (–) (n = 29)	P-value
	Mean (SD)/Median (IQR)			
Age [years]	59.9 (9.4)	63.0 (7.6)	51.4 (8.6)	< 0.001
Male, n [%]	82 (74.6)	59 (72.8)	23 (79.3)	0.62
BMI [kg/m^2]	27.4 (3.6)	27.3 (3.8)	27.7 (2.9)	0.96
CHA_2DS_2-VASc score	1.0 (1.0–3.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	0.0006
LA diameter [mm]	42.7 (3.3)	42.9 (3.4)	42.1 (3.1)	0.17
LVEF [%]	61.2 (4.9)	61.2 (5.0)	62.8 (4.5)	0.15
CHF, n [%]	3 (3.3)	3 (3.7)	0 (0)	0.56
Hypertension, n [%]	83 (74.1)	65 (80.3)	16 (55.2)	0.010
Diabetes, n [%]	23 (20.5)	20 (24.7)	3 (10.3)	0.12
Vascular disease, n [%]	12 (10.7)	10 (12.4)	2 (6.9)	0.51
LCPV trunk, n [%]	18 (16)	8 (9.9)	8 (27.6)	0.031
RMPV, n [%]	20 (17.9)	11 (13.6)	9 (31.0)	0.0498
Persistent AF, n [%]	9 (8)	7 (8.6)	2 (6.9)	1.0
Anticoagulation duration [months]	32.0 (21.5)	34.8 (17.6)	24.2 (28.6)	0.001
Time from diagnosis [months]	36.0 (24.0–48.0)	36.0 (26.0–48.0)	28.0 (20.0–44.0)	0.030
CRP [mg/L]	0.99 (0.38–2.82)	1.0 (0.4–2.8)	0.9 (0.3–2.9)	0.47
BNP [pg/mL]	49.1 (25.5–91.3)	51.2 (30.1–92.0)	42.1 (21.4–78.0)	0.21
Urea [mg/dL]	40.1 (9.7)	40.5 (10.31)	38.9 (7.54)	0.47
Creatinine [mg/dL]	0.9 (0.2)	0.9 (0.22)	0.9 (0.21)	0.75
eGFR [mL/min]	81.7 (14.3)	80.3 (14.44)	85.8 (13.43)	0.075
RBC [×10^12/L]	4.8 (0.4)	4.7 (0.45)	4.9 (0.38)	0.12
WBC [×10^9/L]	7.1 (1.7)	7.3 (1.77)	6.7 (1.54)	0.13
HCT [%]	43.3 (3.5)	43.2 (3.53)	43.8 (3.41)	0.36
HGB [g/dL]	14.4 (1.1)	14.3 (1.1)	14.7 (1.16)	0.15
PLT [×10^9/L]	224.1 (61.0)	224.6 (60.40)	222 (63.53)	0.90
MPV [fL]	8.8 (1.6)	8.8 (1.54)	8.7 (1.74)	0.70
PCT [%]	0.2 (0.1)	0.2 (0.06)	0.2 (0.06)	0.73

*Data presented as mean (SD) or median (IQR). AF — atrial fibrillation; BNP — brain natriuretic peptide; BMI — body mass index; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; HCT — hematocrit; HGB — hemoglobin; LA — left atrium; LV — left ventricle; LCPV — left common pulmonary vein; MPV — mean platelet volume; PLT — platelets; PCT — plateletcrit; RBC — red blood cells; RMPV — right middle pulmonary vein; WBC — white blood cells

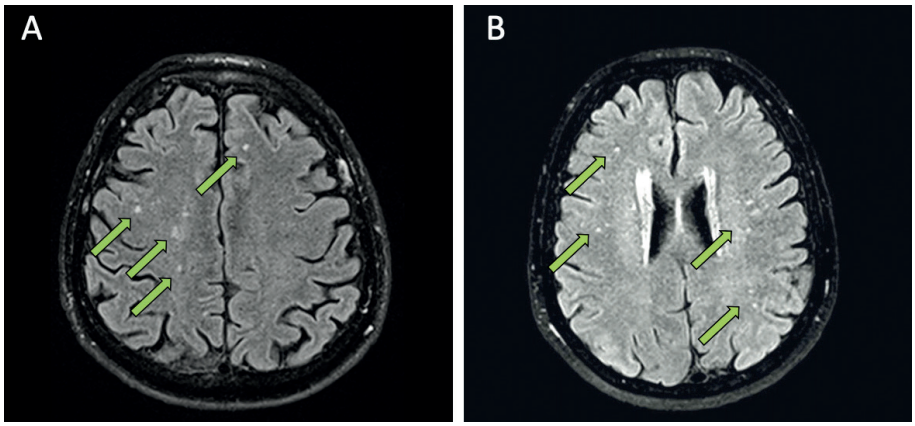

Figure 1. MRI-detected (FLAIR sequence) disseminated hyperintense cerebral lesions localized in frontal and parietal lobe white matter in two ablation-naïve patients with non-valvular atrial fibrillation (**A** and **B**)

Table 2. Uni- and multivariable analysis of silent cerebral ischemic lesion incidence in ablation-naïve AF patients

Parameter	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age [years]	1.2 (1.1–1.3)	< 0.001	1.2 (1.13–1.34)	< 0.0001
Male, n [%]	0.7 (0.3–1.9)	0.49		
BMI [kg/m^2]	0.96 (0.8–1.1)	0.56		
CHA_2DS_2-vasc score	2.2 (1.3–3.4)	0.0013		
LA diameter [mm]	1.1 (0.95–1.2)	0.28		
LV ejection fraction	0.9 (0.85–1.0)	0.15		
CHF, n [%]	–	1.0		
Hypertension, n [%]	3.3 (1.3–8.2)	0.01		
Diabetes, n [%]	2.8 (0.8–10.4)	0.11		
Vascular disease, n [%]	1.9 (0.4–9.2)	0.43		
LCPV trunk, n [%]	0.29 (0.1–0.9)	0.026	0.11 (0.025–0.52)	0.005
RMPV, n [%]	0.35 (0.13–0.96)	0.05		
Persistent AF, n [%]	1.3 (0.25–6.5)	0.77		
Anticoagulation duration [months]	1.03 (1.0–1.05)	0.023		
Time from diagnosis [months]	1.01 (0.99–1.04)	0.26		
CRP [mg/L]	1.0 (0.9–1.1)	0.68		
BNP [pg/mL]	1.0 (0.99–1.0)	0.33		
Urea [mg/dL]	1.02 (1.0–1.1)	0.47		
Creatinine [mg/dL]	1.4 (0.2–10.8)	0.74		
EGFR [ml/min]	0.97 (0.9–1.0)	0.078		
RBC [×10 ^ 12/L]	0.45 (0.2–1.3)	0.13		
WBC [×10 ^ 9/L]	1.2 (0.9–1.6)	0.13		
HCT [%]	0.9 (0.8–1.1)	0.36		
HGB [g/dL]	0.7 (0.5–1.1)	0.15		
PLT [×10 ^ 9/L]	1.0 (1.0–1.0)	0.9		
MPV [fL]	1.1 (0.8–1.4)	0.70		
PCT [%]	3.78 (0.002–6050.8)	0.72		

AF — atrial fibrillation; BMI — body mass index; BNP — brain natriuretic peptide; CI — confidence interval; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; HCT — hematocrit; HGB — hemoglobin; LA — left atrium; LV — left ventricle; LCPV — left common pulmonary vein; MPV — mean platelet volume; OR — odds ratio; PLT — platelets; PCT — plateletcrit; RBC — red blood cells; RMPV — right middle pulmonary vein; WBC — white blood cells

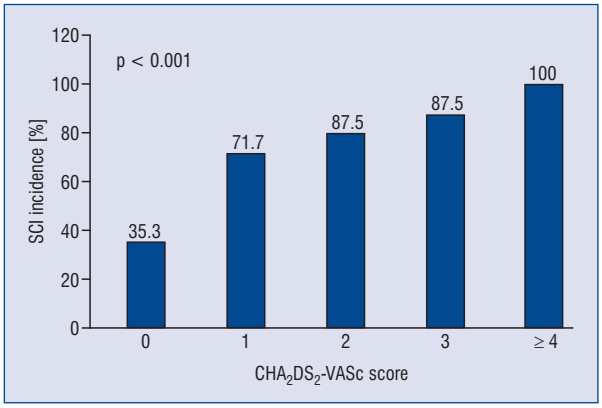

Figure 2. Incidence of silent cerebral ischemic lesions

stroke risk factors, which is consistent with the recently published data [28]. Interestingly, incorporation of pre-existing silent cerebral lesions into the CHA_2DS_2-VASc score calculation may alter the risk-benefit ratio of anticoagulation [29], and new multi-factor risk scales are being proposed [30]. Moreover, in the studied population a trend towards association of decreased eGFR and increased BNP with SCILs was observed. This is consistent with the data published by Kim et al. [31], who reported kidney dysfunction as an independent risk factor for the presence and number of SCILs in generally healthy adults, and by Matusik et al. [32], who demonstrated the prothrombotic and antifibrinolytic

alterations in AF patients with stage 4 chronic kidney disease irrespective of clinical stroke risk factors, as well as with the increased NT-proBNP level [33].

Can specific pulmonary vein anatomy be a predictor for SCILs in the AF population?

In our group, multivariable logistic regression analysis identified the presence of an anatomical variant of common trunk of left-sided pulmonary veins as a negative predictor for MRI-detected brain lesions. The typical configuration of pulmonary veins is characterized by 2 pulmonary veins with separate ostia on each side of the left atrium, and it can be found in approximately 70% of the general population. The common ostium of both left-sided veins (left common trunk) is the most frequent (about 30%) anatomical variant of PV anatomy, and the second is the presence of one or more additional (usually right-sided) pulmonary veins [34]. There are no reports linking pulmonary vein anatomy and risk of thromboembolic events, except for pulmonary arteriovenous malformation, but in such cases the phenomenon of paradoxical embolism is the obvious cause of stroke [35]. Nevertheless, because the atrial fibrillation itself is a well-known risk factor for thromboembolic events, we can hypothesize that the gap in the link between PV anatomy and MRI-detected silent brain lesions can be filled with the anatomy-dependent arrhythmia burden. Indeed, there are several published reports on the association between the PV anatomy and susceptibility to atrial arrhythmias. The weak point of this theorem is the fact that in most papers a positive correlation between anatomical variants of pulmonary venous drainage and AF incidence is reported [36–39]. Interestingly, the anatomical variation usually linked with AF susceptibility is the presence of additional/ /multiple right-sided veins [36], which is not always true for the presence of common ostia, and some authors use the general term of "atypical anatomy" to analyze its potential role as the risk factor for AF occurrence. In a recently published paper [39], the authors reported a positive correlation between the anomalies of pulmonary veins (in general) and AF occurrence. However, when only the presence of common ostia (both left- and right-sided) was considered, the opposite trend was demonstrated: a common ostium was identified less frequently in the AF group compared to the control group (11% vs. 15%) [39]. Perhaps the "anatomical anomaly" itself should not be considered as an AF risk factor, but simply the total number of pulmonary veins instead. The fewer pulmonary veins (and thus less complicated atrial anatomy), the fewer triggers (and possibly also less substrate) to initiate and sustain atrial fibrillation. This hypothesis finds extra support in the reports demonstrating positive correlation between left atrial diverticula (also referred to as additional appendages) and AF occurrence [40–42]. Obviously, this is only one possible explanation of our findings, and the potential "protective" effect of the anatomical variant of PV common trunk against thromboembolic events clearly needs further investigation.

Limitations of the study

There are several limitations of our study. Firstly, it is a single-center analysis, performed on a relatively low number of patients, which may constrain our capacity to draw substantial conclusions. Secondly, the duration of oral anticoagulation may differ between the analyzed patients, depending on their additional thromboembolic risk factors, reflected in the CHA_2DS_2-VASc score, which could have an impact on the incidence of MRI-detected silent brain lesions but in the opposite way to our findings, considering that high CHA_2DS_2-VASc values are a strong indication of permanent oral anticoagulation. Thirdly, our study was conducted on a group of patients referred for AF ablation and consequently did not include patients in a rate-control strategy with persistent long-lasting AF nor with extremely enlarged atria, because these groups would probably not benefit from the ablation procedure. Therefore, caution is needed when converting our findings to the general AF population.

Conclusions

In the present study, we were able to demonstrate that MRI-detected silent cerebral ischemic lesions are frequent in the population of patients with symptomatic non-valvular atrial fibrillation, naïve to invasive cardiac intervention. The incidence of SCILs is higher in patients with a long history of arrhythmia and with higher CHA_2DS_2-VASc score. The relationship between the anatomy of pulmonary veins and the incidence of SCILs needs further investigation.

Data availability statement: The data underlying this article will be shared upon reasonable request to the corresponding author.

Ethics statement: The study conforms to the guiding principles of the Declaration of Helsinki,

the study protocol was approved by institutional review board (approval number KE-0254/292/2012), and all patients gave informed consent before the procedures.

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Author contributions: AG and MO conceptualized the article. PM, KWoj, KWys, and AnnJ were responsible for data curation. AG and MJ established the methodology and performed the analysis. AG, AT, and AW administered and supervised the project. AG, MJ, AndJ, KK, and MO were responsible for validation. AG and MJ visualized the results. AG, AT, KK, and MO wrote the original draft. MJ, PM, KWoj, KWys, AW, AnnJ, and AndJ reviewed and edited the paper. All authors have read and agreed to the final version of the manuscript.

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