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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

AssesSment of the left atrial appendage morphoLogy in patients aAfter ischaeMic Stroke — the ASSAM study protocol

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Abstract

Stroke remains the most dangerous and frightening complication of atrial fibrillation (AF). A causal relationship between ischaemic stroke and atrial arrhythmias such as AF or atrial flutter has been well established. Numerous factors predisposing to peripheral embolism in patients with AF have been well established and included in the CHA_2DS_2-VASc score. Although proper anticoagulation minimises the risk attributable to "known" risk factors, stroke may still occur. Thus, "unknown" risk factors may play an important role in stroke risk stratification in patients with AF. We assume that one of the important "unknown" risk factor is the left atrial appendage morphology. The ASSAM study is planned to include 100 patients after ischaemic stroke or transient ischaemic attack (TIA) and known status of anticoagulation at the time of stroke. The control group will consist of 100 patients scheduled for AF ablation without a history of stroke or TIA.

Key words: left atrial appendage, stroke, atrial fibrillation

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INTRODUCTION

Stroke remains the most dangerous and frightening complication of atrial fibrillation (AF) [1]. A causal relationship between ischaemic stroke and atrial arrhythmias such as AF or atrial flutter remains undoubtable [2, 3]. Numerous factors predisposing to peripheral embolism in patients with AF have been well defined, documented, and included in the CHA_2DS_2-VASc score [4]. Although proper anticoagulation minimises the risk attributable to "known" risk factors, stroke may still occur. Thus, "unknown" risk factors may play an important role in stroke risk stratification in patients with AF [5].

Virchow's triad has been well recognised as the explanation of circumstances leading to peripheral artery thrombosis [6]. Left atrial (LA) thrombosis probably has a similar background with slightly different factors leading to its occurrence. In this setting, blood stasis is caused by AF due to lack of contractibility of LA, concomitant diseases facilitating thrombus formation, and specific anatomical area — LA appendage (LAA) predisposes to thrombosis (Fig. 1).

It has been shown recently that specific types of LAA anatomy may facilitate stroke occurrence whereas other types of LAA morphology may play a preventive role. However, data from these studies are conflicting and there are several limitations concerning the methodology of these studies. Korhonen et al. [7] found a significantly increased prevalence of ChickenWing morphology in patients with stroke compared to the matched controls. This was also previously suggested by Kimura et al. [8]. However, in the Di Biase et al. [9] study, non-ChickenWing morphology was the most prevalent LAA type in stroke patients, whereas Anselmino et al. [10] suggested an association between CauliFlower and WindSock morphologies and silent cerebral ischaemia. Differences in the results of these studies may be due to variable classification of LAA morphology used by the authors and also due to a lack of data on anticoagulation status at the time of stroke. There are studies describing LAA anatomy in a different manner; however, in the vast majority of them the analysis was based on anatomical specimens 1:1 [11, 12]. Herein, we would like to present the study protocol that investigates the role of LAA anatomy in thrombus formation in a well-defined population of patients with known anticoagulation regimen at the time of the event.

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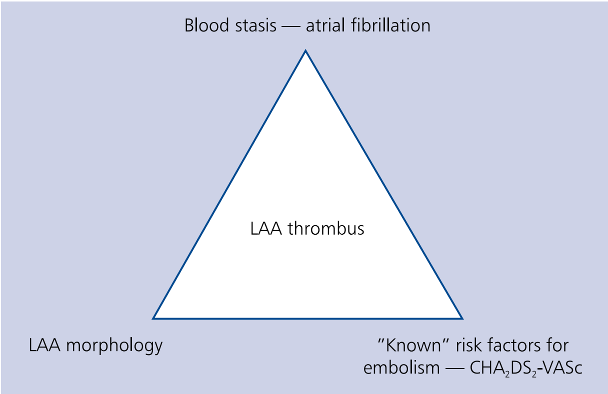

Figure 1. Modified Virchow's triad, suggested cause of the left atrial appendage (LAA) thrombus formation

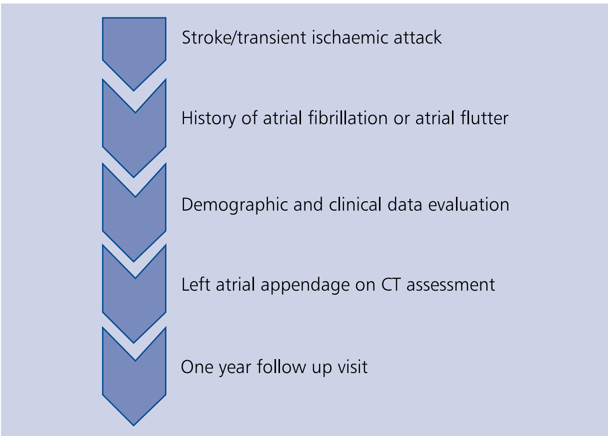

Figure 2. Design of the study; CT — computed tomography

Hypothesis

The LAA morphology in patients with an elevated risk of peripheral thromboembolism defined as CHA_2DS_2-VASc score > 2 is one of the risk factors for ischaemic stroke.

METHODS

Objective and variables

To assess the risk of ischaemic stroke in different types of morphology of the LLA.

Demographic and clinical variables will be analysed (Table 1).

Table 1. Demographic and clinical data

Age
Sex
Date of stroke/TIA event
CHA_2DS_2-VASc score:
Heart failure history
Hypertension
Age > 75 years
Diabetes mellitus
Stroke/TIA history
Vascular disease
Age 65–74 years
Female
HAS-BLED score:
Hypertension history
Renal disease
Liver disease
Stroke history
Prior major bleeding or predisposition to bleeding
Labile INR
Age > 65 years
Medication usage predisposing to bleeding
Alcohol or drug usage history
Date of first AF episode
Type of AF:
Paroxysmal
Persistent
Persistent long standing
Permanent
NYHA class
Weight [kg]
Height [cm]
Body mass index
History of tobacco smoking
Drugs before ischaemic episode
Drugs after ischaemic event — during inclusion
Laboratory tests when ischaemic event occurred
Echo study data

AF — atrial fibrillation; INR — international normalised ratio; NYHA — New York Heart Association; TIA — transient ischaemic attack

Study population: inclusion/exclusion criteria

The study population will consist of 100 patients after ischaemic stroke or transient ischaemic attack (TIA) (study group) and 100 patients scheduled for AF ablation without a history of ischaemic stroke or TIA (control group). Study flow chart is presented in Figure 2.

Inclusion criteria (study group) include: ischaemic stroke or TIA and history of AF/atrial flutter and known status of anticoagulation at the time of stroke (treatment dose, international normalised ratio level).

Exclusion criteria (any) include: haemorrhagic stroke, serious renal impairment with glomerular filtration rate < 30 mL/min, hyperthyroidism, allergy to the contrast agent, mental inability to sign the informed consent, receptive aphasia.

Assessment of LAA morphology

The assessment will be performed by one radiologist (IM) and one electrophysiologist (JB), who are experienced in in-

Table 2. Anatomic variation of left atrial appendage (LAA) morphology assessed by computed tomography

Morphology of LAA:
Chicken wing
Wind sock
Cauliflower
Cactus
Length of LAA
Volume of LAA
Number of LAA sub lobes
The angle of first bend
The distance from the ostium to the first bend
Area of LAA ostium
Shape of LAA ostium
Volume of left atrium
Left atrial diameter (sagittal and coronal axis)

terpreting computed tomography (CT) images. In the case of discordant opinions on LAA morphology, the decision regarding LAA morphology will be made by a senior investigator (PK). Investigators will assess CT images blindly without knowledge of patient allocation to the study subgroups. The analysis of anatomy and measurements of LA size will be performed on 1-mm slices using commercially available software (Leonardo, Siemens Medical Systems). The analysed anatomical parameters are listed in Table 2.

The morphology of LAA will be divided into four types:

— the chicken wing — LAA with only one lobe, its length exceeds 40 mm and its bend angle is less than 100 degrees;
— the windsock — LAA with one dominant lobe (length > 40 mm) and several secondary, or even tertiary ones, its length exceeds 40 mm, and its bend angle exceeds 100 degrees;
— the cauliflower — LAA with a variable number of lobes with lack of a dominant lobe, its total length is less than 40 mm;
— the cactus — LAA with a dominant central lobe with several secondary ones, its total length less than 40 mm.

Assessment of the morphology of the LAA will be performed using volume rendered post-processing and multiplanar reconstruction techniques. The presence or absence of LAA thrombus will also be assessed by CT.

Imaging protocol

Computed tomography angiography will be performed with a dual-source CT scanner (Somatom Definition Flash; Siemens Medical Solutions, Erlangen, Germany) using prospective electrocardiogram (ECG) gating, with detector collimation of 128 × 0.6 mm, a gantry rotation time of 280 ms, tube voltage of 100–120 kV, and tube current of 280–380 mAs depending on the patient's body mass. Highly iodinated contrast material (≥ 350 mg/mL) will be administered in the antecubital vein in the amount of 70–80 ml, using a power injector, at a flow rate of 5 mL/s, followed by a 30-mL saline chaser. Image acquisition will be initiated 5 s after reaching 100 HU threshold enhancement within the region of interest placed in the LA. Prospective ECG-gated examinations will be centred at the best diastole phase of the R-R interval. Patients will not receive beta-blockers for regulation of heart rate.

Statistical analysis

Descriptive, univariate and multivariate analyses will be performed. Data will be presented as frequencies and percentages for categorical variables and as means + standard deviations (normally distributed variables) or medians and inter-quartile ranges ($25–75^{th}$) (skewed distribution) for continuous variables. The comparison between groups will be made using the χ^2 test (or Fisher exact test where appropriate) for categorical variables and the independent t-test or Mann-Whitney rank test for continuous variables, as appropriate. Collinearity between variables will be assessed using Pearson or Spearman correlation coefficient, as appropriate. Multiple stepwise logistic regression analysis will be performed to test the impact of morphology of the LAA (potential predictors) on stroke and corrected for known confounders. The predictors of stroke identified in univariable analysis ($p < 0.1$) will be introduced as independent variables into multivariable models. In case of close (strong) correlation between independent variables, only the strongest univariate predictor will be entered into the selection procedure. Variables with skewed distribution will be transformed prior to analyses. Finally, receiver operating characteristic curves will be constructed and c-statistics (area under curve) will be determined to evaluate the value of specific findings to predict stroke. A two-sided p-value < 0.05 will be considered statistically significant. All analyses will be conducted using SAS 9.2 (SAS Institute, Cary, NC, USA) software.

The sample size was calculated based on the assumption that the risk of stroke/TIA differs between various LAA morphologies from 4% to 18% [9]. At the alfa level of 0.05 and beta level of 0.9, the required number of patients in each group is 100. Thus, the minimal total number of patients is 200.

DISCUSSION

The present study will bring new important data on the relationship between LAA morphology and the risk of stroke or TIA in patients with AF. If the results of the study are positive — a specific type of LAA morphology will be identified as a risk factor for stroke/TIA, which should have an impact on clinical practice and establish the role of CT in identification of patients who are at risk of LAA thrombosis and subsequent stroke/TIA. It may be speculated that the assessment of LAA morphology might play a role in the primary and secondary prevention of stroke/TIA in the future.

Limitations of the study

Firstly, there are known limitations of CT in the assessment of LAA structure, and the analysis performed by an investigator, even a very experienced one, is always subjective. To minimise these limitations, we will use a high-quality, modern CT machine and software, rigorously stick to definitions describing different LAA anatomies, and rely on experienced expert opinion. Secondly, although the study will prospectively recruit patients with a history of ischaemic stroke, data concerning their medication at the time of stroke will be derived from the patient's files, which may influence the accuracy. Thirdly, although in patients with AF the majority of ischaemic strokes are due to thrombus migration from LAA to the central nervous system, other causes of stroke could not be excluded.

Conflict of interest: *none declared*

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Ocena związku wystąpienia udaru niedokrwiennego mózgu z morfologią uszka lewego przedsionka — protokół badania ASSAM

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Streszczenie

Udar niedokrwienny mózgu pozostaje nadal najniebezpieczniejszym i budzącym obawy powikłaniem migotania przedsionków (AF). Związek przyczynowo-skutkowy występowania tego powikłania z arytmiami przedsionkowymi, takimi jak AF i trzepotanie przedsionków został bardzo dobrze opisany. Zdefiniowano wiele czynników, które zwiększają ryzyko zatorowości obwodowej, opisanych za pomocą skali CHA_2DS_2-VASc. Mimo że odpowiednio prowadzona antykoagulacja zmniejsza ryzyko powikłań zakrzepowo-zatorowych wynikających ze znanych czynników ryzyka, udary niedokrwienne nadal się zdarzają. Dlatego wydaje się, że również inne, nie do końca poznane czynniki ryzyka powinny być brane pod uwagę w stratyfikacji ryzyka udaru u pacjentów z AF. Zakładamy, że jednym z tych jeszcze niepoznanych czynników ryzyka może być morfologia uszka lewego przedsionka. Do badania ASSAM zostanie włączonych 100 pacjentów po przebytym udarze niedokrwiennym lub przejściowym niedokrwieniu mózgu, u których w momencie tego zdarzenia znany będzie poziom leczenia przeciwkrzepliwego. Grupa kontrolna zostanie sformowana ze 100 pacjentów, u których zaplanowano wykonanie ablacji podłoża AF, ale bez wywiadu przebytego udaru mózgu.

Słowa kluczowe: uszko lewego przedsionka, udar niedokrwienny, migotanie przedsionków

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