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Letter to the Editor

Right Hemispheric Predominance of Brain Infarcts in Atrial Fibrillation: A Lesion Mapping Analysis

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Dear Sir:

Atrial fibrillation (AF) increases the risk of an ischemic stroke three- to five-fold,[1] and cardioembolic strokes are associated with worse outcomes than strokes of other origin.[2] Covert brain infarcts occur in more than a third of patients with AF and have been associated with cognitive impairment.[3] Regional distribution of brain infarcts may explain why most patients with AF and brain infarcts on neuroimaging have no clinical history of stroke or transient ischemic attack (TIA). Previous studies on a possible side-predominance of brain infarction in patients with AF have yielded conflicting evidence and were mostly done in patients with clinically manifest stroke.[4] In the present study, we systematically analyzed the anatomical distribution and localization of covert and overt brain infarcts according to different vascular territories in a large cohort study of patients with established AF.

This is a cross-sectional analysis of the Swiss-AF cohort, a prospective, multicenter cohort study of unselected patients with AF across 14 centers in Switzerland.[5] In total, the study has enrolled 2,415 participants with AF. At baseline visits, brain magnetic resonance imaging (MRI) was acquired in all patients (without contraindications for MRI) on either a 1.5 or a 3.0 Tesla scanner, depending on the participating site. The most frequent reason for missing MRI was the presence of an implanted cardiac device (n=461). The 1,716 patients with eligible baseline brain MRI data (mean age 73±8 years, 27% women, 20% with history of stroke or TIA) were included in the present study (Supplementary Table 1). Detailed methodological descriptions are provided in the Supplementary methods.[3,5-11] Briefly, we manually segmented brain infarcts on MRI. Lesions were classified into large non-cortical or cortical infarcts (LNCCIs) and small non-cortical infarcts (SNCIs).[7] LNCCIs were considered infarcts of potentially embolic or atherothrombotic ori-

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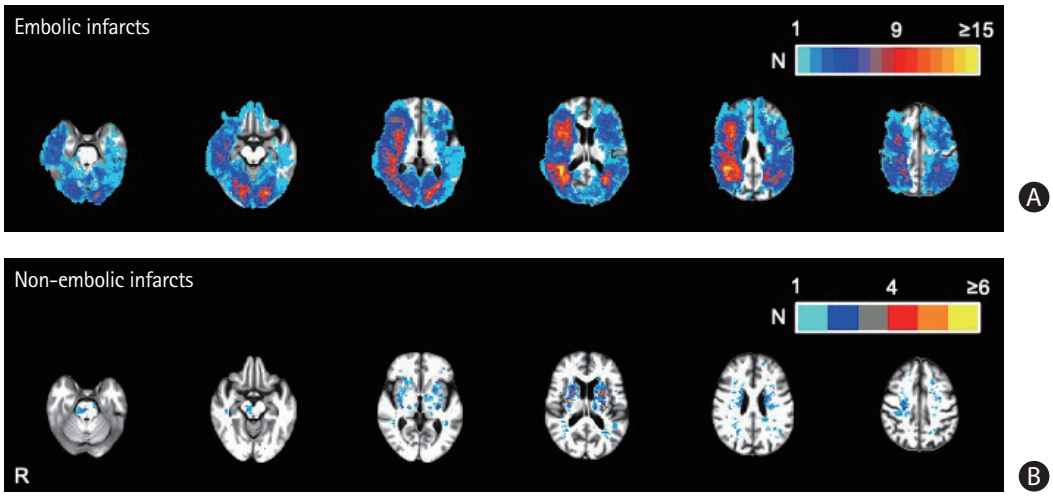

Figure 1. The distribution of infarcts. Figure depicting the voxel-based sum of all large cortical and non-cortical infarcts and small non-cortical infarcts overlaid on an age-specific standard brain template. The color scale indicates the number of patients with an infarct in a given voxel.

gin and included large non-cortical infarcts with a diameter of >20 mm, and cortical infarcts of any size. SNCIs were considered infarcts of potentially microangiopathic origin and defined as lesions with a diameter of ≤20 mm not involving the cortex. Lesion masks were co-registered separately to an age-specific brain template and overlaid to compute a voxel-based probability map.

We observed LNCCIs in 386 (22%) patients. Visually, in the voxel-based probability map, a clear right-hemispheric preponderance was observed (Figure 1A). Results of the statistical comparison of lesion counts, average lesion volumes, and percentages affected per vascular territory are reported in Supplementary Table 2. LNCCIs were most often located in the territory of the middle cerebral artery (MCA). While, in the MCA territory, LNCCI counts were evenly distributed between the hemispheres (Wilcoxon matched-pair rank test; P=0.796), the average volume of infarcts was significantly larger in the right compared to the left hemisphere (left [total]: 512.4 mL vs. right [total]: 1,240.1 mL; Wilcoxon matched-pair rank test; P=0.002). Similarly, the percentage of the MCA territory affected by LNCCIs (calculated by the proportion of lesional voxels per vascular territory per patient) was significantly larger in the right than in the left hemisphere (Wilcoxon matched-pair rank test; P=0.008). No side-preponderance of LNCCIs was detected for the vascular territories of the anterior and posterior cerebral arteries. No side-difference was observed for SNCIs (Figure 1B).

Our findings might indicate, that large emboli preferentially hit the right brain hemisphere. We hypothesize that both vascular anatomy (i.e., the right artery originating more proximally from the heart) and the physical properties of cardiac emboli (i.e. their size) contribute to the right-sided preponderance for embolic cerebral infarcts. The right common carotid artery originates more proximally from the heart and with less angulation from the aortic arch, which in turn increases the likelihood of these large emboli to enter the right carotid artery. This may especially be the case for larger cardiac emboli which are dragged to the outer curvature of the aorta. This hypothesis is supported by a study using anatomically accurate models of the human aorta and their branch arteries.[12]

As no information on competing stroke etiologies was collected in SWISS-AF, we cannot know how many LNCCIs might have been of potential atheroembolic origin, which represents a major limitation of our study. However, it is unlikely that the observed asymmetry in LNCCIs is explained by atherosclerosis of the aortic arch or supra-aortic arteries.

A better understanding of the localization in relation to the size of brain infarcts might be helpful in clinical routine. Focal symptoms and signs originating from right hemispheric lesions may easily be missed by patients and physicians. The proportion of patients with a history of clinically manifest stroke or TIA was consistent with previous population-based studies in AF,[1] but 37,1% of patients had an ischemic infarct on MRI (SNCI or LNCCI combined). We have previously shown that covert brain infarcts have a significant impact on cognitive decline in AF,[3] and are associated with an increased risk of future strokes.[13] Whether routine brain MRI screening in patients with AF improves risk stratification remains to be elucidated by future prospective studies.

Supplementary materials

Supplementary materials related to this article can be found

online at https://doi.org/10.5853/jos.2021.03531.

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Supplementary methods

Study population

The Swiss Atrial Fibrillation (Swiss-AF) study is a prospective cohort study which has enrolled 2,415 participants with established atrial fibrillation (AF) in 14 centers in Switzerland. The detailed study design and first results have been reported previously.[3,5] Included patients were ≥65 years old and had either paroxysmal AF defined as: self-terminating AF lasting <7 days that does not require cardioversion and that was documented at least twice within the last 60 months; persistent AF defined as AF sustained ≥7 days and/or re-quiring cardioversion, documented within the last 60 months; or permanent AF. Additionally, a smaller group of patients between 45 and 65 years of age was included to assess the effects of AF on actively employed individuals. Patients with a secondary form of AF or unable to provide informed consent were excluded.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the local ethics committees (Ethikkommission Nordwest- und Zentralschweiz), and written informed consent was obtained from all participants (Trial Registration: ClinicalTrials.gov Identifier, NCT02105844).

Image acquisition

Baseline brain magnetic resonance imaging (MRI) was acquired on either a 1.5 or a 3.0 Tesla scanner, depending on the participating site. The standardized protocol has been described in detail previously.[3,5] Of relevance for the present study, 3D T1-weighted (T1w) magnetization prepared rapid gradient echo (MPRAGE; spatial resolution 1.0×1.0×1.0 mm^3), and 2D axial T2-weighted fluid attenuated inversion recovery (FLAIR; spatial resolution 1.0×1.0×3.0 mm^3) sequences. Out of the 2,415 patients enrolled in Swiss-AF, complete baseline MRI was available in 1,748 patients. The most frequent reason for missing MRI was the presence of an implanted cardiac device (n=461, 69%).

Lesion segmentation

Lesion segmentation was performed on FLAIR images by professional medical image analysts at the Medical Image Analysis Center (MIAC AG, Basel, Switzerland), blinded to clinical and other information, according to in-house standard operating procedures approved for international clinical phase III trials.[6] Board certified neuroradiologists confirmed all ratings. Lesions were classified into large non-cortical or cortical infarcts (LNCCIs) and small non-cortical infarcts (SNCIs). LNCCIs were considered infarcts of potentially embolic origin and included (1) large non-cortical infarcts with a diameter of >20 mm, and (2) cortical infarcts defined as hyperintense lesions on FLAIR involving the cortex irrespective of their size. SNCIs were defined as hyperintense lesions on FLAIR ≤20 mm in diameter assessed on axial sections and not involving the cortex.[7]

Image registration

To prepare images for image co-registration, the patients' brain data were first extracted from the T1w images using FreeSurfer v6.0 (binarization of 'aseg.auto' output from 'recon-all' pipeline; https://surfer.nmr.mgh.harvard.edu/fswiki). Resulting brain masks were dilated slice-by-slice by two voxels since less restrictive brain extraction yielded better results in the later registration. Secondly, corresponding T2w FLAIR white matter hyperintense lesions and LNCCIs were filled on T1w images to minimize their effect on image registration. This was done using the lesion filling algorithm encoded in FSL[5] and masking of the lesion portions in the grey matter.

For image registration (FSL v5.0, FMRIB's Software Library; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki), FLAIR images were first linearly registered to T1w images using FSL (FMRIB's linear registration tool, FLIRT; using defaults settings, 6 degrees of freedom).[8,9] The transformation parameters resulting from this image registration were then applied to the SNCI and LNCCI lesion masks (FLAIR image contrast) using a nearest-neighbor interpolation. At this step, the skull was removed from the FLAIR-to-T1w images using the previously prepared brain masks. Then, FLAIR-to-T1w images were non-linearly registered to an age-specific standard brain template from the BRAINS image bank (https://www.brainsimagebank.ac.uk/; for brains early to mid-seventies; spatial resolution 1.0×1.3×1.0 mm^3) using FSL (FMRIB's non-linear registration tool, FNIRT; settings as specified in the provided configuration file, taking as reference the age-specific brain template).[10] The resulting transformation parameters were then applied to the transformed FLAIR-to-T1w lesion masks again using nearest-neighbor interpolation. The quality assessment of the registration was done by trained and experienced raters. If images showed strong distortions in the registered images, patients were excluded from subsequent analyses. At image registration, 32 patients were excluded, leaving 1,716 patients (98%) for the present analyses.

Spatial lesion distribution and mapping onto vascular territories

The co-registered LNCCI and SNCI lesion masks were overlaid on the age-specific brain template to generate voxel-based le-

sion probability maps. Lesion masks were then projected onto the co-registered MNI Vascular Territories Atlas.[11] Number and volume of lesions within anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA) territories, were computed. Moreover, the percentages of vascular territories affected by LNCCIs or SNCIs (i.e., percentage overlay) were calculated.

Statistical analyses

Infarct counts, volumes, and percentages were reported. We tested if these measures differed within vascular territories of left and right brain hemispheres. The Wilcoxon matched-pair rank test was used to compare median differences of infarct counts, volumes, and percentages within ACA, MCA, and PCA. Only patients having an infarct in this specific vascular territory—either in the left or the right hemisphere—were considered. No correction of *P*-values for multiple testing was performed due to the exploratory nature of the analysis. All statistical analyses were done in R version 3.6.3. (https://www.r-project.org/).

Data availability statement

The patient informed consent forms, as approved by the responsible ethics committee, do not allow the data to be made publicly available. The participants signed a consent form, which states that their data, containing personal and medical information, are exclusively available for research institutions in an anonymized form. Researchers interested in obtaining the data for research purposes can contact the Swiss-AF scientific lead. Contact information is provided on the Swiss-AF website (http://www.swissaf.ch/contact.htm). Authorization of the responsible ethics committee is mandatory before the requested data can be transferred to external research institutions.

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Supplementary Table 1. Baseline characteristics of patients

Variable	Value
Age (yr)	72.5±8.4
Female sex	471 (27.4)
Comorbidities	
History of hypertension	1,186 (69.1)
History of diabetes	267 (15.6)
History of stroke	228 (13.3)
History of stroke/TIA	343 (20.0)
History of CAD	455 (26.5)
History of PVD	122 (7.1)
History of sleep apnea	234 (13.6)
Oral anticoagulation	
NOAC	922 (53.7)
VKA	625 (36.4)

Values are presented as mean±standard deviation or number (%).
TIA, transient ischemic attack; CAD, coronary artery disease; PVD, peripheral vascular disease; NOAC, non-vitamin K oral anticoagulant; VKA, vitamin K antagonist.

Supplementary Table 2. Infarcts per vascular territory in all patients

LNCCI	Total count		Count			Total volume (mL)		Infarct volume (mL)			Percentage		
	Left	Right	Left	Right	*P*	Left	Right	Left	Right	*P*	Left	Right	*P*
ACA	229	248	1 (0–11)	1 (0–16)	0.999	138.5	91.1	0 (0–17.5)	0 (0–3.8)	0.279	0.0 (0–11.8)	0.0 (0–6.3)	0.367
MCA	449	438	1 (0–23)	1 (0–23)	0.796	512.4	1240.1	0 (0–28.4)	0.2 (0–38.8)	0.002	0.0 (0–13.3)	0.1 (0–27.1)	0.008
PCA	383	426	1 (0–30)	1 (0–34)	0.996	207.5	208.8	0 (0–4.1)	0 (0–10.8)	0.872	0.0 (0–26.0)	0.0 (0–24.7)	0.834

Values are presented as median (interquartile range). Number and volume of infarcts within left or right ACA, MCA, and PCA are shown. The variable 'volume' corresponds to the total infarct volume per vascular territory in all patients. The variable 'infarct volume' refers to the average infarct volume within a vascular territory (if there are multiple infarcts per patient and territory). Moreover, the percentages of vascular territories affected by the infarcts is reported (corresponds to the proportion of lesional voxels per vascular territory per patient). The Wilcoxon matched-pair rank test was used to compare median differences of infarct counts, volumes, and percentages between hemispheres. Only patients having an infarct in this specific vascular territory—either in the left or the right hemisphere—were considered.
LNCCI, large non-cortical or cortical infarct; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.