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## Selective vulnerability of Cortical Border Zone to microembolic infarct

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Subjects' code: Magnetic Resonance Imaging [58], Embolic Stroke [53]

Keywords: silent cortical ischemia; microembolic infarct; cortical border zone

## Abstract

Background and Purpose: Endovascular procedures, including atrial fibrillation transcatheter ablation, may cause microembolization of brain arteries. Microemboli often cause small sized and clinically silent cerebral ischemias (SCI). These lesions are clearly visible on early post-operative magnetic resonance (MR) diffusion-weighted images (DWI). We analyzed SCI distribution in a population of patients submitted to atrial fibrillation transcatheter ablation.

Methods: 78 out of 927 consecutive patients submitted to transcatheter ablation were found positive for acute SCI on a post-operative MR. SCI were identified and marked and their coordinates were transformed from native space into the International Consortium for Brain Mapping (ICBM) / Montreal Neurological Institute (MNI) space. We then computed the voxel-wise probability distribution map of the SCI using the Activation Likelihood Estimation (ALE) approach.

Results: SCI showed a strong prevalence for cortex. In supratentorial regions, SCI selectively involved cortical border zone between Anterior, Middle and Posterior Cerebral Arteries; in infratentorial regions, distal territory of Postero-Inferior Cerebellar Artery. Possible explanations include selective embolization, linked to the vascular anatomy of pial arteries supplying those territories, reduced clearance of emboli in a relatively hypoperfused zone, or a combination of both. This particular distribution of lesions has been reported in both animal models and in patients with microemboli of different sources.

Conclusions: We demonstrated a selective vulnerability of cortical border zone to microemboli due to atrial fibrillation transcatheter ablation. We hypothesize that such selectivity could apply to microemboli of different sources.

## Introduction

Cerebral ischemic lesions are an unwanted consequence, due to microemboli produced during arterial catheterization, of intravascular procedures ranging from less invasive ones (i.e.: diagnostic cerebral angiography) to neurovascular or cardiovascular therapeutic procedures<sup>1</sup>. In particular, in atrial fibrillation transcatheter ablation ischemic lesions are related to the energy application protocol, type of ablation device and amount of anticoagulation, all conditions that may facilitate periprocedural formation of emboli<sup>2</sup>.

Post procedural lesions are visible as hyperintense spots on diffusion-weighted magnetic resonance images (DWI), ranging from some millimeters to less than a centimeter. Hyperintensity on DWI images only lasts some days<sup>3</sup>, allowing to identify the lesion as acute and to set a precise temporal relationship with the procedure. The small size of lesions implies that causative emboli are small enough to pass without consequences through the major intracranial vessels and occlude only small peripheral arteries, an hypothesis supported by the fact that the majority of those emboli has a diameter of about 10-120 micron<sup>4</sup>.

The majority of these lesions are clinically silent in the short term (Silent Cerebral Ischemia, SCI), although long-term effects in particular for large number of lesions, remain unknown. Since structure of the brain is highly heterogeneous, location of a lesion is a major factor for symptoms development, but a precise topographic analysis in terms of probability of each cerebral area of being affected by SCI has not been done up to now.

To address this issue, in this study we analyzed a population of patients with SCI due to atrial fibrillation transcatheter ablation, to describe the topography of lesions as related to different brain structures and to territories of major arteries.

## Materials and Methods

### Study population

We included 927 consecutive patients undergoing transcatheter ablation for paroxysmal or persistent atrial fibrillation (as defined by the 2010 European Society of Cardiology Guidelines <sup>5</sup>) in two high volume centers with experienced cardiac electrophysiology laboratories from January 2009 to June 2012. To rule out alternative sources of embolism, 14 patients with known major brain vessel disease or previous stroke diseases were excluded from analyses (identified by a previous echo doppler, CT angiography, angiography or by anamnesis).

To assess the presence of lesions, all the patients underwent to a pre- and post-procedure brain MR examination, including an axial fluid-attenuated inversion recovery (FLAIR) and a DWI (see Supplementary Materials for patients' selection, ablation procedure and parameters of the MR sequences). MR images were analyzed independently by 2 certified radiologists blinded to the clinical status and identity of the patients. The joint agreement was 89% (ICC = 0.72, see Supplementary Materials for details) and conflicts were resolved by common agreement. The presence of even 1 hyperintense spot, not seen on pre-ablation MR, possibly allocated the subject within the SCI group.

A neurological examination including sensory, motor, locomotion, coordination, cranial nerves, mental status, language and reflexes investigation, was done before and after ablation procedure.

Only patients with at least a new DWI lesion and no changes in pre- and post-procedure neurological examination were included in the SCI group.

All patients gave informed consent, in accordance with Helsinki declaration, and the local ethical committees of both centers approved the study.

### **Data preprocessing and analysis**

To obtain the coordinates and sizes of the SCI we used the following pipeline for all the patients:

- 1) An expert radiologist, blind to the clinical status and identity of the patients, reanalyzed all MR images of the SCI group. SCI were identified, marked and measured using the ROI

(Region of Interest) tools of the free software MRICro (<http://www.mccauslandcenter.sc.edu/mricro>).

- 2) The coordinates of the centers of SCI were transformed from native space in the same stereotaxic space with the normalization coefficients that morph the subject FLAIR to a FLAIR template <sup>6</sup> in the International Consortium for Brain Mapping (ICBM) / Montreal Neurological Institute (ICBM/MNI) standard space (see Supplementary Materials for normalization algorithm details). Then we classified the SCI using the labeled ICBM template (<http://www.loni.usc.edu/atlasses>) to determine whether each lesion targeted grey matter (GM) or white matter (WM). Each lesion was also classified on the basis of lobar organization: frontal, temporal, parietal, occipital, basal ganglia, thalamic, cerebellar; left (L) or right (R) and anterior (A) or posterior (P) to central sulcus.
- 3) We tested the frequencies of SCI against a uniform distribution for all the above categories to estimate if any brain area contained a greater than chance number of SCI (see Supplementary Materials for the details). Since patients were treated in two different centers, we compared the frequencies of lesions between subgroups with contingency tables and Fisher's exact test, while continuous variable were analyzed using the Mann-Whitney U test. A threshold of  $p < 0.05$  was chosen as significant. All statistical analyses were performed with IBM SPSS Statistics 20.0.

To compute the voxel-wise distributions maps of the SCI we used the Activation Likelihood Estimation (ALE) approach. The ALE analysis is a quantitative meta-analytic method that can be used to estimate consistent activation across different imaging studies <sup>7</sup>. ALE map of coactivations were derived from the coordinates of the peaks of activation. In our study, every subject has been inserted separately, as a single subject experiment, and smoothed with an FWHM of 19 mm, as in the original ALE approach. Regions of convergence were calculated using GingerAle 2.3 software <sup>7,8</sup> in the ICBM/MNI space. For all analyses the selected p threshold was False Discovery Rate <sup>9</sup>

with independence or positive dependence assumption, FDR  $p_{ID} < 0.05$  and minimum clusters extent  $K_e > 200 \text{ mm}^3$ .

## Results

We found 164 SCI (Fig. 1, Supplementary Figure I), sized 2 to 8 mm, in 78 patients (see Table 1 for clinical and demographic data). The relative frequencies of SCI were not different in the Italian and French subgroups, and the two subgroups were homogeneous for clinical and demographic characteristics (see Supplementary Table I, II), therefore we analyzed sample as a whole.

From the comparison of the frequencies of the SCI (Table 2) with an uniform distribution (that is, the probability of finding a SCI is the same for all areas) we inferred two conclusions:

- 1) Regarding general brain architecture, SCI were more frequent in the gray than in white matter ( $p < 0.001$ ).
- 2) Regarding lobar distribution, lesions were more frequent in frontal ( $p = 0.003$ ), parietal lobes ( $p = 0.017$ ) and cerebellum ( $p < 0.001$ ), with relative sparing of insulae and temporal lobes.

These results were confirmed by the observation of the SCI distributions maps (Fig. 2 axial slices, Fig. 3 coronal slices) that showed 9 clusters (Supplementary Table III) in particular in bilateral fronto-parietal cortex and cerebellum. Some clusters also appeared in occipital cortex and in basal ganglia, with sparing of temporal cortex and the limbic areas.

Areas between superficial and deep territories of Middle Cerebral Artery (MCA) and between two adjacent superficial arterial territories of the MCA, Anterior (ACA) and Posterior (PCA) Cerebral Arteries have been defined<sup>10</sup> as “internal” (IBZ) and “cortical border zone” (CBZ), respectively.

The distribution of supratentorial SCI followed the CBZ between the MCA, ACA and PCA territories (Fig. 3), while in cerebellum distal Posterior Inferior (PICA), Anterior Inferior (AICA) and Superior Cerebellar Arteries (SCA) territories were involved, potentially corresponding to border zone between major cerebellar arteries. The IBZ, instead, appeared substantially spared.



## Discussion

Post-procedural SCI did not homogeneously distribute in the brain but followed a precise topography, related to both GM / WM architecture and vascular territories of major arteries of the brain.

Considering the GM / WM architecture, we found that SCI selectively affected the cortex both in infra- and in supratentorial regions. This is not unexpected, since it confirms data from animal experimental models of microembolization <sup>11-14</sup> that showed that the majority of emboli sized 20 to 100 micron remains in superficial pial arteries, while a minority enter perforating vessels and only a few cause cortical ischemia. Moreover, in a series of endovascular procedures in humans, known to cause hyperintense DWI lesions on post-operative MR (see <sup>1</sup> for a review), cortex was found preferentially involved in a few papers where topography of the lesions was analyzed <sup>15</sup>, agreeing with our findings. Local vessel anatomy, and in particular the poor anastomotic collateral of penetrating arterioles <sup>16</sup> explains the prevalence of cortical-subcortical lesions. Selective involvement of the perforating vessels feeding the cortex, as compared with perforating vessels feeding the white matter or basal ganglia is explained by the relatively greater flow reaching the cortex <sup>17</sup>.

In our patients supratentorial lesions clustered on the CBZ between main branches of ACA, MCA, PCA, while infratentorial lesions clustered on the distal territories of PICA, possibly matching border zone between major cerebellar arteries <sup>18</sup>. This selective vulnerability of CBZ to SCI due to transcatheter ablation was not directly demonstrated up to now, and may be explained in different ways related to the particular features of its vascularization. The main pial branches (ACA, MCA and PCA) have their own macroscopic cortical territory of vascularization, but on a microscopic scale, anastomosis between pial arteries on the surface of the brain can lead to wide overlappings between vascular territories of different arteries. The CBZ, receiving dual blood supply from distal

branches of different arteries, was named as “watershed” (‘Grenzflächen infarkte’, oral presentation 1959, Professor K. J. Zülch <sup>19</sup>); the alternative definition as “last meadow” (‘der letzten Wiesen’, <sup>20</sup>), describes in an intuitive way its characteristic of being located at the very end of the feeding vessels. In the posterior fossa, variability of vascular territories of cerebellar arteries makes analysis of vascular territories more difficult.

Being located at the very end of main pial branches, both haemodynamic and embolic mechanism are involved in border zone infarctions. It is well known that border zones, in particular IBZ, are extremely sensitive to severe hypotension <sup>21</sup>. In effect, stenosis of internal carotid artery was found in the majority of patients with border zone infarctions in several series <sup>22,23</sup>; peri-operative hypotension was shown being a relevant risk factor for CBZ infarctions after cardiac surgery <sup>24</sup>. Those conditions were both ruled out in our patients, and could not contribute significantly to our findings. The different SCI probabilities that we found for CBZ and IBZ confirmed previous observations in a large series of brain infarcts <sup>10</sup> where IBZ infarcts were caused mainly by hemodynamic compromise, whereas embolic pathogenesis appears to contribute greatly to CBZ infarcts.

An embolic genesis of CBZ infarcts was first proposed by Pollanen <sup>13,14</sup> which suggested direct selective embolization as cause of CBZ infarct. Relationship between the size of the emboli and diameter of the vessel may cause selective targeting of emboli in vessels feeding the CBZ. Pial vessels divisions are frequently asymmetrical, with one dominant and one secondary branch; trajectory of the emboli in an experimental replica of brain vessels bifurcation depended on the relative size of the embolus and on the relative flow <sup>17</sup>. Roughly, emboli sized more than one quarter of the vessel diameter preferentially get the bigger branch, while smaller emboli distribute proportionally to the relative flow. If this applies to all bifurcations of brain arteries, emboli from 50 to 100 micron distribute proportionally to the flow in large Willisian bifurcations, but in distal bifurcations, they preferentially select the biggest vessel, feeding the most distal territories, the CBZ. Similar considerations may apply distal territories of cerebellar arteries <sup>18</sup>. Several evidences

support this hypothesis: in the particular case of MCA stenosis, Wong et al.<sup>25</sup> demonstrated a prevalence of microemboli in patients with ischemia of CBZ respect to different cortical regions; sources of embolism were identified in the majority of patients with posterior CBZ infarctions by Belden et al.<sup>26</sup>. A different explanation was suggested by Caplan et al.<sup>27,28</sup>: local impairment of flow due to an embolus may be compensated and embolus “cleared out” if blood supply is adequate; if not, it leads to an ischemic lesion. Then clearance of emboli is selectively impaired in locations more prone to be hypoperfused, as CBZ. Hypoperfusion and microembolism probably both concur to CBZ lesions in patients with Moya-Moya disease after brain angiography<sup>29</sup> or hypercoagulability without flow reduction nor microembolism, as in polycitemia vera<sup>30</sup>.

We could not discriminate between the hypotheses of selective embolization versus impaired washout or a combination of both, but our data strongly support the concept of a selective vulnerability of CBZ to microembolic lesions in our particular model.

It remains a matter of debate whether the above considerations also apply to emboli from different sources, allowing the generalization of our considerations to different conditions. To our knowledge, ALE analysis or similar topographic probabilistic approach were never applied to vascular lesions, making it impossible a precise comparison with different models. Anyway, as discussed above, selective vulnerability of CBZ to microemboli was found both in single patients and in particular populations<sup>12,31,32</sup>. Then, common topography of lesions could support common behaviour of emboli. Furthermore, computing the topography of SCI using the location of transcatheter-induced emboli, as in our work, has the positive feature of being unbiased against patients risk factors, as SCI seem to be only marginally influenced by them<sup>2</sup>.

Acute sign of CBZ infarct includes transient symptoms and frequent seizures at onset, transcortical aphasia, discalculia, Gerstmann syndrome, frontal syndrome, lower limb weakness<sup>22,23,33,34</sup>. No gross neurological symptoms developed in our patients, probably because of small size of the lesions, while subtle deficits could have been missed, possibly escaping a basic neurological investigation. Even in largest series, the majority of the lesions were asymptomatic, so that DWI was proposed as

a surrogate marker to estimate neurological injury, due to the rarity of neurological signs and symptoms<sup>35</sup>. Anyway, the consequences of accumulation of large lesions loads may be more relevant in the long term and possibly co-responsible for increased cognitive decline in patients with sources of microemboli<sup>36,37</sup>.

### Limits

The present study had several limitations. First, alternative sources of emboli were not completely ruled out. Strict temporal contingency between ablation and lesions detection suggested a strong causative relationship, but, in any case, our conclusions remain unchanged for microemboli of different sources. Second, technical factors, in particular artifacts, may bias the detection of SCI on DWI, in particular if small. Finally, the absence of a direct imaging of the vessels did not consent to account for individual anatomical variability of vascular system or intracranial arteries pathology that could influence the relative distribution of SCI. The relevant size of the sample allowed ruling out both the above-mentioned limitations, at least partially.

### Conclusions

Atrial fibrillation transcatheter ablation selectively caused cortical lesions that selectively affected supratentorial CBZ and posterior cerebellar lobes. This selectivity may be explained by direct embolization of the most distal cortical branches, by impaired washout of emboli due to the peculiar flow pattern of CBZ, or by a combination of both. Since similar distributions of lesions were described in different models of microembolization of brain, we suggest that infra- and supratentorial border zones are selectively vulnerable to microembolization.

**Disclosures: None**

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## Figures captions

### **Fig. 1: SCI detection on post-procedure MR**

On the left the FLAIR image, on the right the DW image. The SCI was detected in the left postcentral gyrus. Radiological convention (left is right).

### **Fig. 2: SCI distributions maps, axial slices**

ALE maps of coactivations are derived from the coordinates of the peaks of activation. The distribution of supratentorial SCI involved particularly the bilateral fronto-parietal cortexes and the bilateral posterior cerebellum, following the cortical border zone. FDR  $p < 0.05$  and minimum clusters extent  $K_e > 200 \text{ mm}^3$ . We used Mango software (<http://ric.uthscsa.edu/mango/>) for visualizing and saving images, overlaying the GingerAle maps onto a standard ICBM/MNI brain template. Slices in axial direction and neurological convention (left is left).

### **Fig. 3: SCI distributions maps, coronal slices**

ALE maps of coactivations are derived from the coordinates of the peaks of activation. The distribution of supratentorial SCI involved particularly the bilateral fronto-parietal cortexes and the bilateral posterior cerebellum, following the cortical border zone. FDR  $p < 0.05$  and minimum clusters extent  $K_e > 200 \text{ mm}^3$ . We used Mango software (<http://ric.uthscsa.edu/mango/>) for visualizing and saving images, overlaying the GingerAle maps onto a standard ICBM/MNI brain template. Slices in coronal direction and neurological convention (left is left).

**Table 1: Clinic and demographic data**

Sample size N	78
Mean Age [y]	58 ± 12
Sex Male N (%)	63 (81%)
Hypertension N (%)	50 (64%)
Diabetes N (%)	6 (8%)
Structural heart disease N (%)	
Absent	62 (79%)
CAD	6 (8%)
HCM	1 (1%)
VCM	1 (1%)
CHF	8 (10%)
Dyslipidemia N (%)	25 (32%)
AF paroxysmal N (%)	45 (58%)
AF persistent N (%)	30 (38%)
AF persist long-standing N (%)	3 (4%)
Mean LVEF %	59% ± 9%
Warfarin or NOACs N (%)	54 (69%)
CHA <sub>2</sub> DS <sub>2</sub> -VASc score* N (%)	
0	17 (22%)
1	28 (36%)
≥2	33 (42%)
Source of energy N (%)	
Radiofrequency	72 (92%)
Cryoenergy	6 (8%)

## Type of lesion N (%)

PVI	78 (100%)
Left isthmus	35 (45%)
Roof line	26 (33%)
CFAE	18 (23%)

Procedure time [min]	175 ± 71
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Values are mean ± SD or counts (%). \*The CHA<sub>2</sub>DS<sub>2</sub>-VASc score consists of congestive heart failure or left ventricular dysfunction, hypertension, age, diabetes, stroke or transient ischemic attack, thromboembolism, and vascular disease. AF = Atrial Fibrillation, CAD = coronary artery disease, HCM = hypertrophic cardiomyopathy, VHD = valvular heart disease, CHF = congestive heart failure, LVEF = left ventricular ejection fraction, NOACs = novel oral anticoagulants (Dabigatran), PVI = pulmonary veins isolation, CFAE = complex fractionated atrial electrograms

**Table 2: SCI frequencies**

Area	GM	WM	Left	Right	Cortex	Cerebellum	A	P
N	<b>139</b>	<b>25</b>	87	77	98	<b>34</b>	48	50
	<b>(85%)</b>	<b>(15%)</b>	(53%)	(47%)			(49%)	(51%)
							)	)
Area	Frontal	Parietal	Tempora	Occipita	Limbic	Basal Ganglia	Thalamus	
			1	1				
N	<b>46</b>	<b>31</b>	<b>1</b>	17	<b>3</b>	5	2	
	<b>(47%)</b>	<b>(32%)</b>	<b>(1%)</b>	(17%)	<b>(3%)</b>			

Counts (%) GM = gray matter, WM = white matter, A = anterior, P = posterior,  
in red bold greater than chance, in italic black bold lower than chance