Illustrated atlas of post - AF ablation cerebral abnormalities

Illustrated Atlas of post-AF Ablation Cerebral Abnormalities

Fiorenzo Gaita MD Prof*, Maria Consuelo Valentini MD Prof §, Laura Corsinovi MD PhD*, Martina Pianelli MD*, Davide Castagno MD*, Federico Cesarani MD °, Marco Scaglione MD ^.

* Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza Hospital, University of Turin, Italy

§ Division of Neuroradiology, Città della Salute e della Scienza Hospital, University of Turin, Italy

° Division of Radiology, Cardinal Guglielmo Massaia Hospital, Asti, Italy

^ Division of Cardiology, Cardinal Guglielmo Massaia Hospital, Asti, Italy

Word count: 2407 words, 2 table, 8 figures, 40 references

Key words: atrial fibrillation, atrial fibrillation trans-catheter ablation, cardioembolic risk, cognitive decline, silent cerebral ischemia, magnetic resonance imaging.

Disclosure: none

Corresponding author:

Fiorenzo Gaita, MD Professor (fiorenzo.gaita@unito.it)

Department of Medical Sciences

Division of Cardiology, Città della Salute e della Scienza Hospital

University of Turin

Corso A.M. Dogliotti 14, 10126 Italy

Phone: +39-011-6335570 Fax: +39-011-6966015

Synopsis

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and relates to high morbidity and mortality due to thromboembolic events, especially ischemic stroke. During the last fifteen years, transcatheter ablation has emerged as an effective therapeutic option to treat AF but carries a risk of possible complications. The occurrence of cerebrovascular accidents, both symptomatic and silent, is one of the most frequent and severe. Transcatheter AF ablation entails a relevant risk of silent cerebral ischemia (SCI) detected by means of Magnetic Resonance Imaging and many efforts have been directed to improve the safety of this procedure.

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias affecting 1-2% of the worldwide population and its burden is expected to rise in the next decades[1,2]. Prevalence of AF increases with age, from less than 0.4% at 40-50 years of age up to 15% over the age of 80[3,4]. Independently from the presence of comorbidities, AF relates to enhanced mortality and thromboembolism[5], particularly to the brain.

The cerebral thromboembolic damage secondary to AF may be clinically overt or appear as a silent phenomenon[6]. If symptomatic brain damage is easily diagnosed and has been thoroughly analyzed, the relationship between AF and silent cerebral ischemia (SCI) needs further evaluation.

SCI have been proven not to be "really silent" from a clinical point of view and to deserve attention by the worldwide medical community, especially as possible complication of transcatheter ablation[7].

As a matter of fact, the presence of silent cerebral damage resulted in a higher incidence of stroke, physical disability, death and with cognitive function worsening[8,9,10] In addition, a recent study[11] underlined that the greater SCI burden typical of patients with AF can negatively impact neuro-psychological performance as compared with a control group.

Cerebral ischemia and Atrial fibrillation ablation

During the last fifteen years, transcatheter ablation of AF has emerged as an effective therapeutic option to restore sinus rhythm (SR), relieve symptoms and prevent thromboembolic events in patients refractory or intolerant to antiarrhythmic medications[12].

As any invasive procedure AF ablation carries a risk of possible complications, whose the occurrence of cerebrovascular accidents is one of the most frequent and severe.

If the incidence of clinically relevant brain alterations following AF ablation can reach 0.9% [13], the occurrence of SCI is much more common and ranges from 7 to 50%. This broad variation can be

attributed to the different patient characteristics, anticoagulation protocol and type of energy used to perform the ablation among different studies[14-17].

Patients clinical characteristics such as age [18,19], previous episodes of AF[20], presence of pre-ablation SCI [21], coronary artery disease, left ventricular hypertrophy or dilatation[14] as well as procedural aspects [i.e. intraprocedural cardioversion , activated clotting time (ACT) <250sec [7], complex fractionated atrial electrograms[18]] were associated with the occurrence of SCI following transcatheter ablation.

Being SCI related not only to AF itself but also to AF transcatheter ablation performed indeed to cure this arrhythmia, our group, as other research teams, tested different interventional protocols, ablation tools and energy sources , in order to minimize the occurrence of such complication.

The anatomical features and distribution of SCI occurring following transcatheter ablation represent a crucial and unresolved issue and need to be further investigated. In addition, if these lesions persist or disappear at follow-up [21,22] and their effective clinical impact remain still unclear and represent a matter of debate[23]. Although computed tomography (CT) scans were previously performed to evaluate the possible occurrence of post AF ablation brain alterations [24-26] , more recently, magnetic resonance (MR) imaging has become the preferred technique used to investigate this problem because of its high sensitivity and accuracy.

Accordingly, fruitful collaborations between cardiologists and neuro-radiologists have been started in many centers in order to achieve thorough cerebral MR scans analyses of patients with AF.

The aim of this article is to discuss the current knowledge about post-AF ablation cerebral abnormalities with particular attention towards their MR features.

Research Protocol on Cerebral ischemia following AF ablation

In our experience we examined by means of cerebral MR imaging a large population of about 900 AF patients undergoing AF transcatheter ablation, of which a group resulted that was affected by SCI following this intervention.

In general, in all the studies focusing on cerebral ischemia following AF ablation performed by our group, all patients included were evaluated by the protocol summarized below:

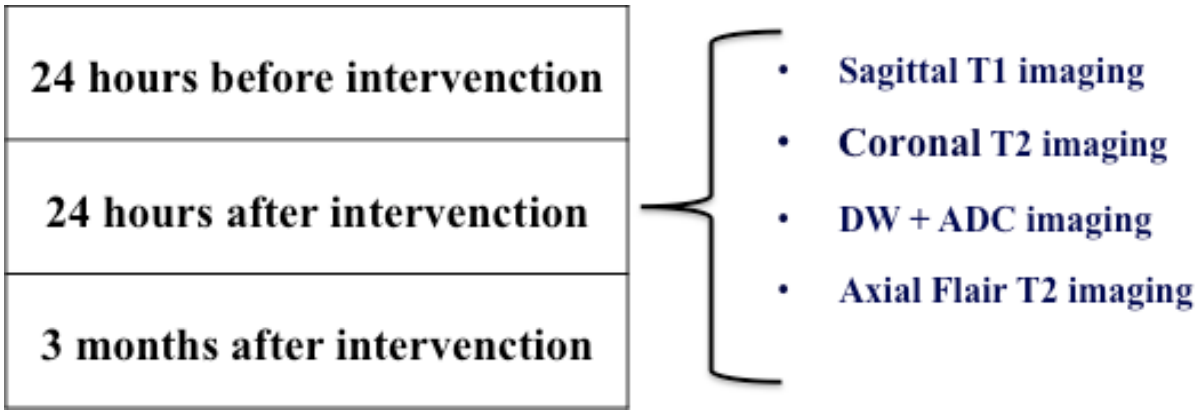
- Medical history (specifically focused on AF subtype and duration, comorbidities and presence of underlying structural heart disease).
- Thromboembolic risk assessment performed by means of systematic calculation of $CHADS_2$[27] and CHA_2DS_2VASc[28] scores.
- Pharmacological history (in particular focused on the anticoagulation regimen used).
- Standardized neurological examination based on the National Institute of Health Stroke Scale (NIHSS Scale) administered by certified neurologists (at the time of admission, after the neuroimaging investigation and during follow-up) in order to exclude clinical signs and symptoms suggestive of focal or global deficits.
- Echocardiographic assessment (both transthoracic and transesophageal).
- MR scans were performed one day before and the day following the ablation. All MRI scans were collected and assessed by two certified neuroradiologists blinded to clinical details. Eventually, a sub-group of patients underwent follow-up MR after 3 months.
- Evaluation of cognitive function by means of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[29].
- Different ablation technologies and protocols were evaluated.
- Exclusion criteria have been described elsewhere[7,11].

Cerebral MR imaging protocol and definition of cerebral ischemic lesions following AF transcatheter ablation

The imaging protocol used in our center is summarized in Figure 1.

Brain MRI examinations were obtained with a 8-channel head coil on Magnetom Avanto® 1,5 Tesla (Siemens, Erlangen, Germany) following an imaging protocol including a sagittal T1- and Coronal T2-weighted spin echo sequence (repetition time/echo time 400/13 msec) and an axial T2-Fluid Attenuated Inversion Recovery [FLAIR] (repetition time/echo time 8500/112 msec; TI, 2500 msec) scan, with a 240 mm field of view, 5 mm section thickness and 154x256 matrix. A diffusion-weighted (DW) and an ADC (apparent diffusion coefficient) mapping sequences with a single shot spin echo with echo-planar imaging technique (repetition time/echo time 3200/99 msec, field of view 230 mm, matrix 128x128, bandwidth 1502 Hz, gradient strength 22 mT, duration of diffusion gradient 31 msec, gradient separation 42 msec in 3 orthogonal directions, acquisition time 43 seconds) was also used.

Figure 1 Magnetic Resonance Imaging (MR) research protocol; DW: diffusion weighted; ADC: apparent diffusion coefficient.



A standardized definition of AF ablation-related Silent Cerebral Ischemia unfortunately is still lacking. In our studies an acute embolic lesion was defined as a focal hyperintense area on T2-FLAIR sequences or isointense in T1-weighted images, not present at the pre-procedural scan, corresponding to a restricted diffusion signal in the DW sequence and confirmed by ADC mapping to rule out a shine-through artifact[7].

Peri-vascular spaces were differentiated from small (<3 mm) lacunar ischemic lesions on the basis of their location, form, surrounding gliosis and T2-FLAIR weighted sequences [30] (the former appearing as hypointense the latter as hyperintense). Leukoaraiosis was defined as bilateral and either patchy or diffuse areas of hyperintensity on T2- and hypointense on T1-weighted MRI sequences confined to the periventricular regions or extending into the centrum semiovale[31].

Size and localization of the focal lesions were recorded according the classification showed in Table 1.

Table 1. Anatomical classification and brain distribution of silent cerebral ischemia.

Dimensions	• Small (<5 mm) • Medium (≥5 and < 10 mm) • Large (≥10 mm)
Cerebral Hemisphere	• Right hemisphere • Left hemisphere
Brain Region	• Frontal lobe • Parietal lobe • Temporal lobe • Occipital lobe • Cerebellum

	• Basal ganglia • Nucleus caudatus • Internal capsula • Corpus callosum
Brain tissue depth	• Cortical region • Subcortical white matter • Deep white matter

Main findings of the studies

The prevalence of SCI reported in our studies ranges from 5 to 38.9%: more details on SCI incidence and different ablation protocols and techniques tested by our group are given in Table 2.

SCI showed a cortical and bilateral distribution with a typical preferential localization within the context of the parietal and frontal lobes as well as in the cerebellum.

Table 2. Silent cerebral ischemia (SCI) incidence following atrial fibrillation trans-catheter ablation in our different studies. Pts: patients. ACT: activated clotting time; RF: radiofrequency; PVAC: pulmonary veins ablation catheter associated with duty-cycled radiofrequency generator.

Pts (n)	**Anticoagulation protocol**	**Source of energy used**	**SCI incidence**	**SCI predictors**
232 [7]	Unfractioned Heparin, ACT > 250 sec	Irrigated RF	14.0%	Cardioversion ACT<250 sec
95 [32]	Unfractioned Heparin, ACT > 250 sec	Irrigated RF	6.0%	Cardioversion
80 [33]	Unfractioned Heparin, ACT > 300 sec	Irrigated RF, Super irrigated RF	7.5% 5.0%	ACT <320 sec
108 [15]	Unfractioned Heparin, ACT > 300 sec	Irrigated RF Cryoballoon PVAC	8.3% 5.6% 38.9%	PVAC

Atlas of cerebral alterations following AF ablation

The following MR images provide some examples of cerebral alterations occurring in patients with different clinical characteristics after AF thranscatether ablation performed with alternative ablation tools.

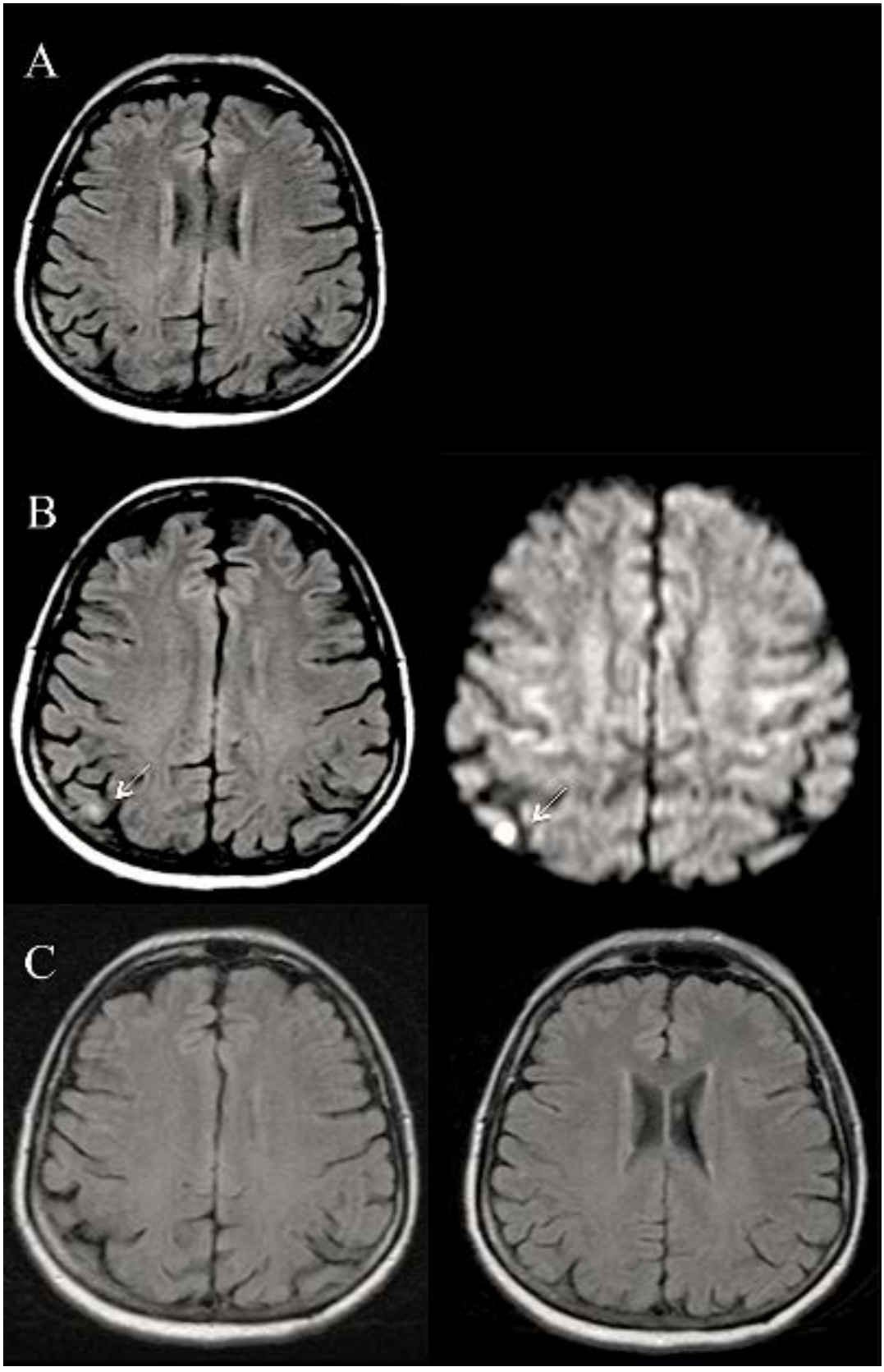
Patient 1

Cerebral MR imaging of a 64 years-old female patient with persistent AF who underwent irrigated RF ablation. (Figure 2).

(A) Pre-procedural scan without brain lesions.

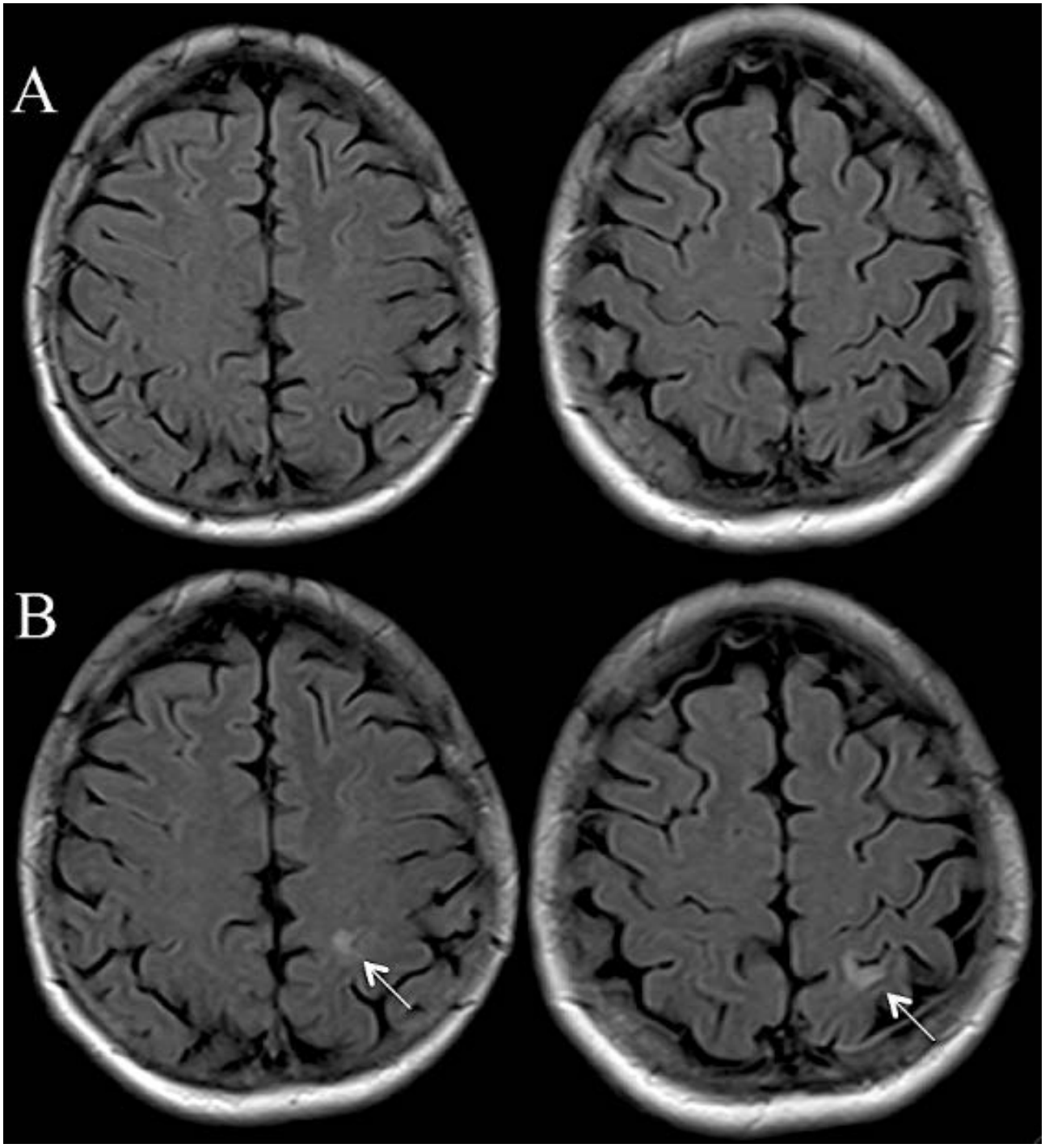
(B) T2- FLAIR and DW images (DWI) post-procedural scans showing the appearance of a single bright cortical lesion in the right parietal lobe (max dimensions 6 x 4 mm) consistent with an acute embolic cerebral infarction (white arrows).

(C) 3 months follow up T2- FLAIR scan demonstrates that the small lesion has disappeared. In order to better visualize the region of interest two adjacent images are provided.


A
B
C

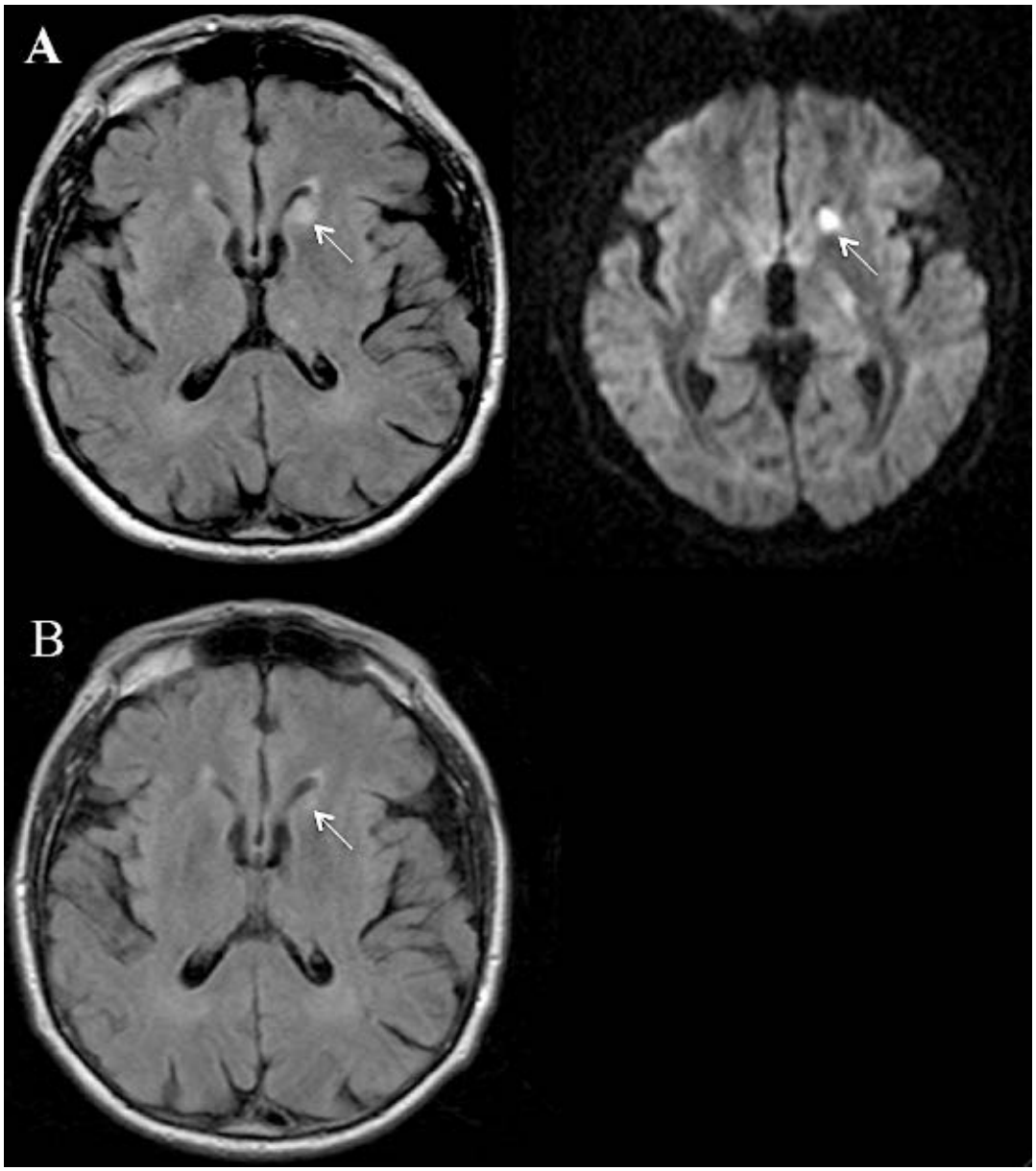
Patient 2

Cerebral MR imaging of 67 years old female patient with paroxysmal AF (Figure 3). MR scans pre (row A) and post RF ablation with PVAC (row B): a new cortical-subcortical single ischemic lesion is present in left parietal lobe (max dimension 10 x 3 mm).



Patient 3

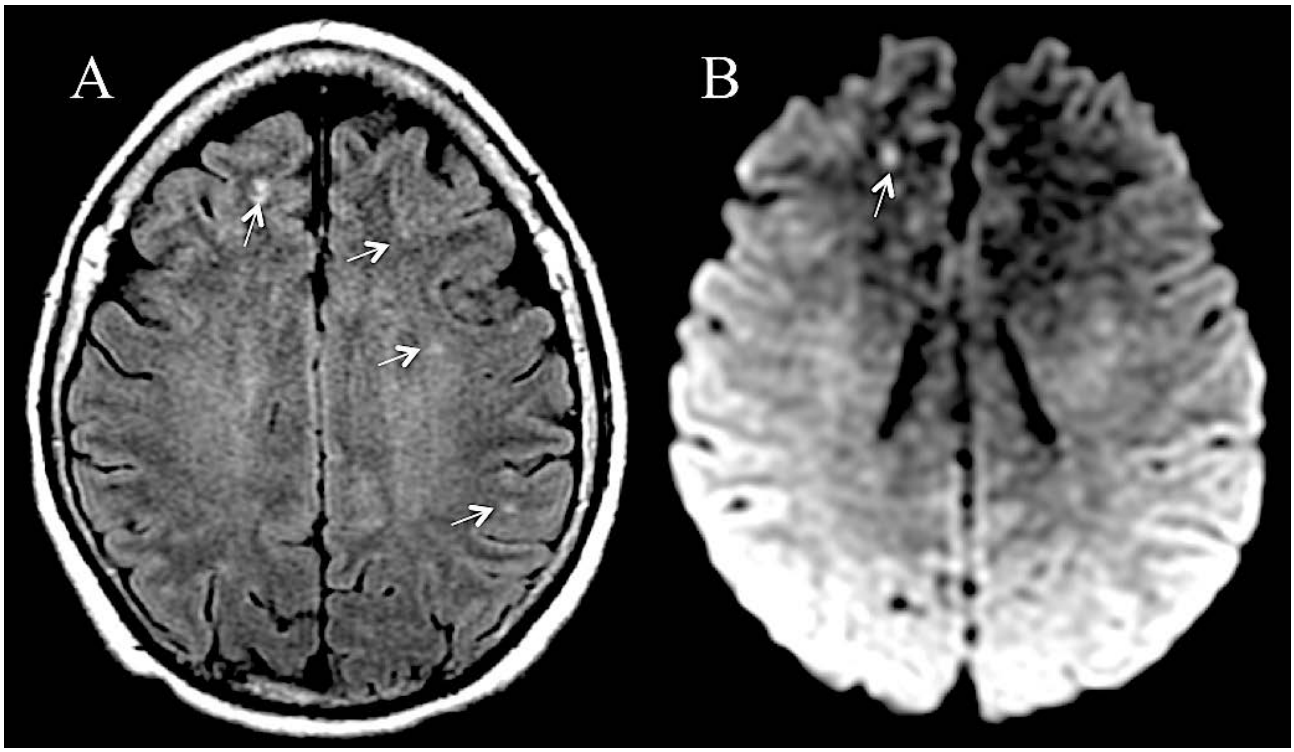
Cerebral MR imaging of a 63 years old male with persistent AF. This is an example of SCI occurring after irrigated RF ablation performed with a mean activated clotting time of 220 sec. Moreover an electrical cardioversion was administered at the end of this procedure (Figure 4). Post-procedural cerebral MRI (row A) T2-FLAIR and DW image indicate a single new ischemic lesion in the left head of the caudate nucleus (white arrows) (max dimensions 4 x 4 mm). Three months follow up T2 FLAIR scans (row B) demonstrated the persistence of a lesion of reduced dimensions.



Patient 4

Cerebral MRI of 71 years-old female, with CHA_2DS_2Vasc score 4, who underwent cryoablation for persistent AF (Figure 5).

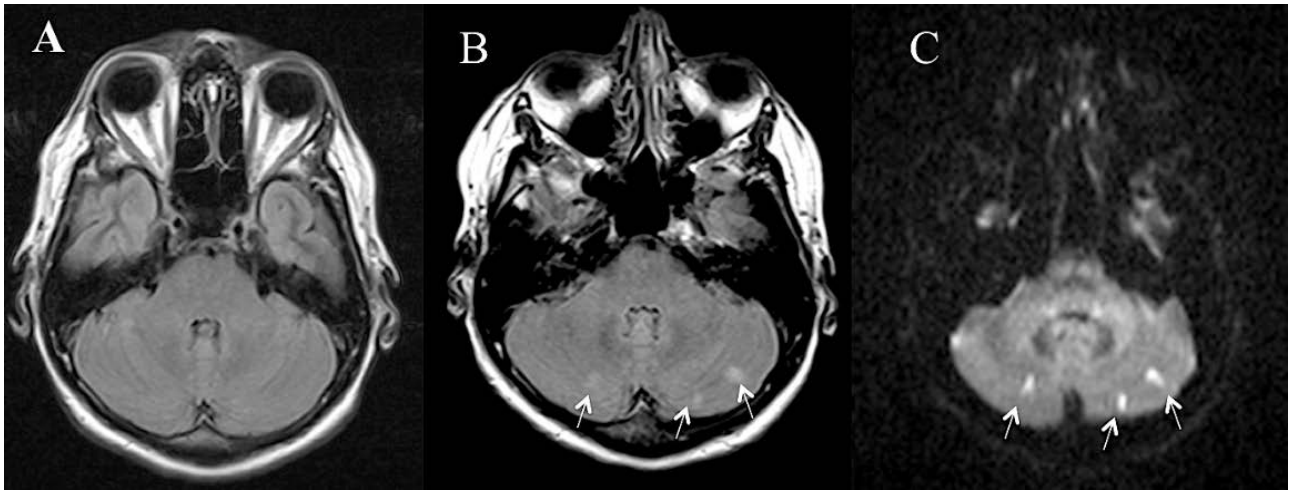
The T2 FLAIR scan (A) demonstrates multiple cortical-subcortical hyperintense cerebral lesions. However only one lesions in the superior frontal gyrus (white arrows) is recent as demonstrated in the DW image (B). The other lesions are attributable to older ischemic brain damage.



Patient 5

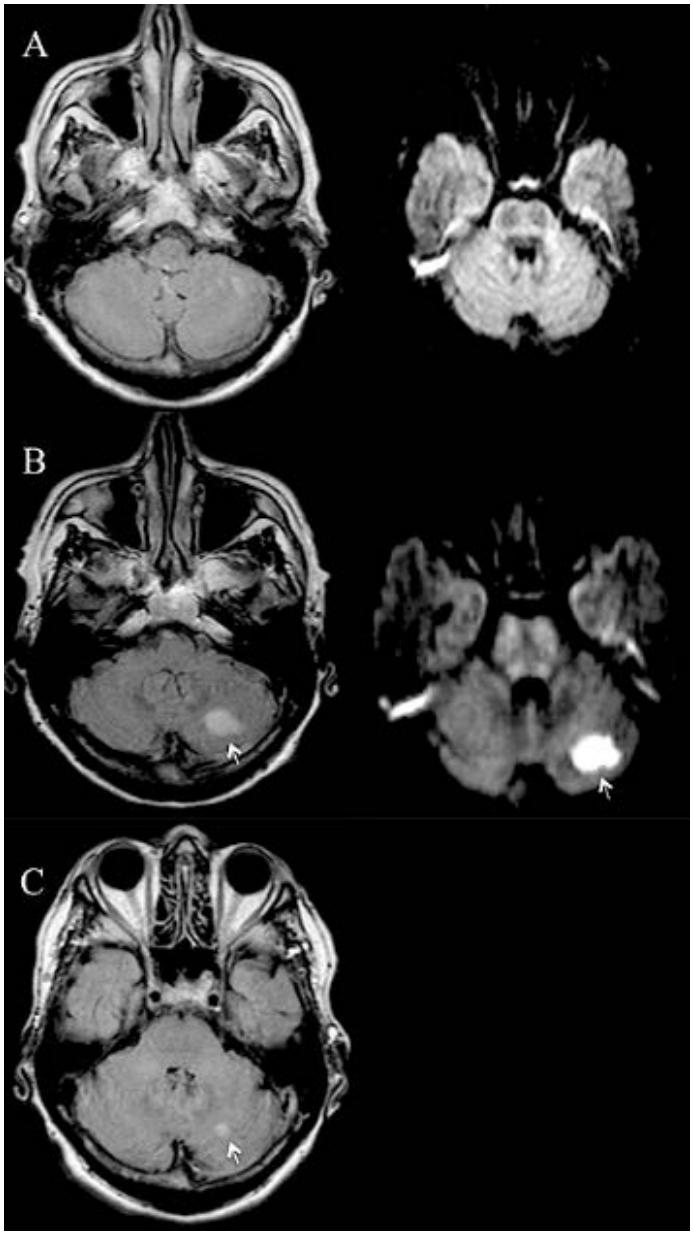
Multiple new ischemic lesions following irrigated RF ablation are visible in the MR scans of a 54 years old-female patient with paroxysmal AF (Figure 6).

Pre-procedural (A), post-procedural (B) T2 FLAIR and post-procedural DW (C): the white arrows indicate new multiple lesions in the left cerebellum (max dimensions 8 x 6 mm).



Patient 6

Cerebral MR imaging of a 59 years-old female with paroxysmal AF and hypertension (Figure 7). In Row A the basal T2 Flair and DWI scans are showed. After irrigated RF ablation (row B) is visible in the right cerebellum a new hyperintense lesion with reduced diffusion (white arrow). After three months of follow up a smaller lesion is still visible in T2-Flair image (row C).

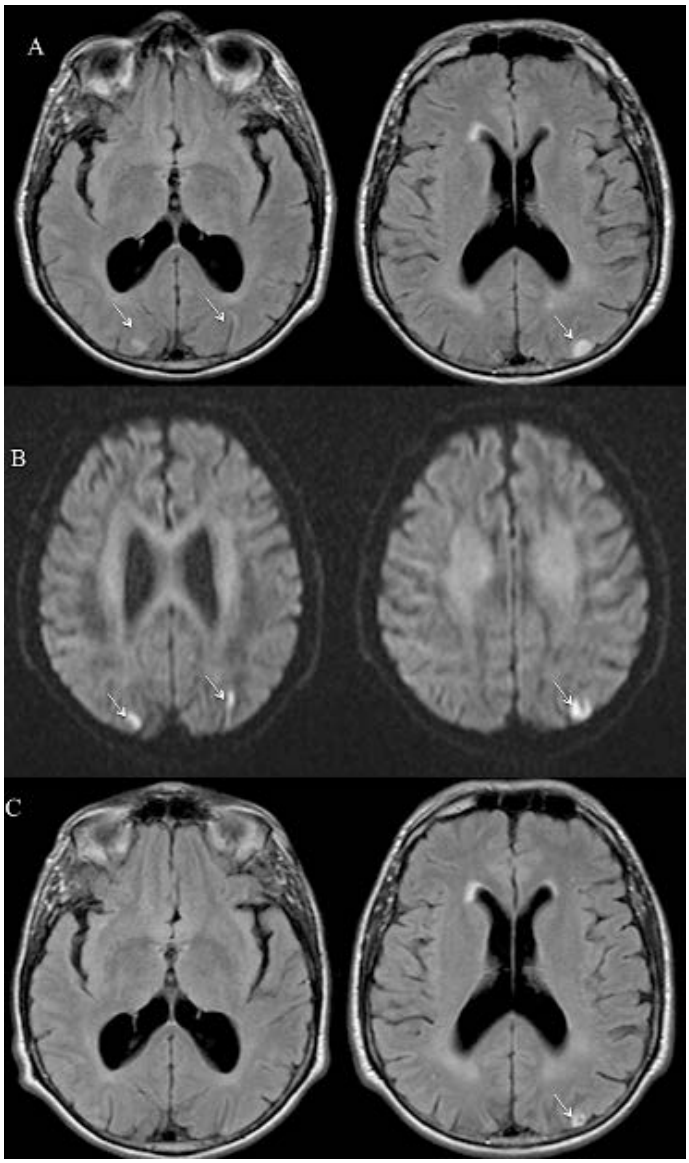


Patient 7

Cerebral scans of 64 years-old male with paroxysmal AF (Figure 8). This is another example of SCI detected after irrigated RF ablation followed by electrical cardioversion at the end of the procedure. The mean activated clotting time was 250 sec.

Post-procedural (row A) T2-FLAIR and DW image (row B) indicate two new bilateral lesions (max dimensions 20 x 10 mm), the first located in right occipital-parietal lobe and the second in the left parietal lobe.

Three months follow up T2 FLAIR scans (row C) demonstrated the disappearance of the first lesion and a reduction of the second one (white arrows).



Considerations regarding silent cerebral ischemia following atrial fibrillation transcatheter ablation.

In our population experiencing silent cerebral ischemia, following AF transcatheter ablation SCI prevalence ranges from 5 to 38,9%: this broad variation depends on the different ablation protocols and tools utilized (activating clotting time value, electrical cardioversion at the end of procedure, type of energy sources applied). Concerning the pathophysiology of silent embolic lesions, three main mechanisms are responsible for the occurrence of SCI during transcatheter ablation: clot formation, char formation and air/gas embolism. In particular, the following are potential causes of thromboembolism: endothelial disruption, electroporation injury, heating of circulating blood elements [34,35] and gaseous[36] or solid embolism due to catheter movement within the left atria.

SCI mostly showed a cortical and bilateral distribution with a typical preferential localization in the parietal and frontal lobes as well as in the cerebellum. These findings are in line with results previously reported by other groups although in smaller study populations. For instance, Schrickel et al[14] outlined a similar distribution of periprocedural cerebral microemboli in the fronto-parietal regions and in the cerebellum in patients with persistent or paroxysmal atrial fibrillation undergoing transcatheter pulmonary vein isolation. The reasons for this preferential localization might be related to the high blood volume and to the vast distribution of the middle cerebral and vertebro-basilar arteries, easily accessed by periprocedural microemboli.

Despite the cortical localization of SCI, none of our patient with post-procedural cerebral alterations had neurological symptoms; this may sound surprising considering that most of the lesions were localized in the cortical region and in the parietal, frontal lobes and cerebellum.

At present the neurocognitive implications of periprocedural SCI still result uncertain and many doubts concerning the persistence or the disappearing of these cerebral lesions at follow up need to be clarified [21,37,38.]

In particular although a large study showed a lower incidence of cerebrovascular events and dementia among AF patients undergoing RF ablation compared with AF patients not treated with ablation [39], other experiences [22,40] highlighted the presence of some cognitive alterations after this type of interventional procedure.

Although we have some information about the neuropsychological significance of SCI due to AF [11] further researches need to be performed in order to fully understand the impact of new cerebral embolic lesions ablation related on cognitive function at long term follow up.

Summary.

Silent cerebral ischemia following transcatheter AF ablation are generally localized in the cortex of the frontal, parietal and cerebellar lobes with about half of the lesions persisting at mid-term follow-up.

It seems to be crucial to continue testing and optimizing AF ablation techniques and protocols in order to reduce their possible embolic complications. In this regard, cerebral MR scans of AF patients has emerged as fundamental evaluation tool.

In addition, it is relevant to create a cardiological and radiological shared knowledge on cerebral damage secondary to AF, being the frequency of these problems already very high and expected to rise in the future decades.

Eventually great attention should be paid to the long-term neurological impact of AF related silent cerebral damage. In the near future, more studies specifically investigating its influence on cognitive function are warranted .

References

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution andgender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995;155:469-73.
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial Fibrillation (ATRIA) study. JAMA 2001;285:2370–5.
3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119–25.
4. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol 2009;104:1534–9.
5. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
6. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007;6:611-9.
7. Gaita F, Caponi D, Pianelli M, Scaglione M, Toso E, Cesarani F, Boffano C, Gandini G, Valentini MC, De Ponti R, Halimi F, Leclercq JF. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. Circulation 2010; 122: 1667-73.

8. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003,348;1215
9. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Dello Russo A, Tondo C, Natale A. Atrial fibrillation and the risk of incident dementia: a meta-analysis. Heart Rhythm. 2012 Nov;9(11):1761-8. doi: 10.1016/j.hrthm.2012.07.026.
10. Asirvatham SJ, Friedman PA. Silent cerebral thromboembolism with left atrial ablation: a lurking danger. J Cardiovasc Electrophysiol 2006; 17:8-10.
11. Gaita F, Corsinovi L, Anselmino M, Raimondo C, Pianelli M, Toso E, Bergamasco L, Boffano C, Consuelo Valentini M, Cesarani F, Scaglione M. Prevalence of Silent Cerebral Ischemia in Paroxysmal and Persistent Atrial Fibrillation and correlation with cognitive function. J Am Coll Cardiol. 2013 Jun 29. [Epub ahead of print]
12. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace 2012; 14(4):528-606.
13. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the

methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010; 3(1):32

14. Schrickel JW, Lickfett L, Lewalter T, Mittman-Braun E, Selbach S, Strach K, Nähle CP, Schwab JO, Linhart M, Andrié R, Nickenig G, Sommer T. Incidence and predictors of silent cerebral embolism during pulmonary vein catheter ablation for atrial fibrillation. Europace 2010; 12:52-7.
15. Gaita F, Leclercq JF, Schumacher B, Scaglione M, Toso E, Halimi F, Schade A, Froehner S, Ziegler V, Sergi D, Cesarani F, Blandino A. Incidence of silent cerebral thromboembolic lesions after atrial fibrillation ablation may change according to technology used: Comparison of irrigated radiofrequency, multipolar nonirrigated catheter and cryoballoon. J Cardiovasc Electrophysiol 2011;22:961-968.
16. Herrera Siklódy C, Deneke T, Hocini M, Lehrmann H, Shin DI, Miyazaki S, Henschke S, Fluegel P, Schiebeling-Römer J, Bansmann PM, Bourdias T, Dousset V, Haïssaguerre M, Arentz T. Incidence of asymptomatic intracranial embolic events after pulmonary vein isolation: comparison of different atrial fibrillation ablation technologies in a multicenter study. J Am Coll Cardiol 2011; 58:681-8.
17. Anselmino M, Matta M, Toso E, Ferraris F, Castagno D, Scaglione M, Cesarani F, Faletti R, Gaita F. Silent Cerebral Embolism during Atrial Fibrillation Ablation: Pathophysiology, Prevention and Management. J Atr Fibrillation 2013; in PRESS
18. Martinek M, Sigmund E, Lemes C, Derndorfer M, Aichinger J, Winter S, Jauker W, Gschwendtner M, Nesser HJ, Pürerfellner H. Asymptomatic cerebral lesions during pulmonary vein isolation under uninterrupted oral anticoagulation. Europace 2012; Oct 24.
19. Neumann T, Kuniss M, Conradi G, Janin S, Berkowitsch A, Wojcik M, Rixe J, Erkapic D, Zaltsberg S, Rolf A, Bachmann G, Dill T, Hamm CW, Pitschner HF. MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary

vein isolation using cryoballoon technique vs. radiofrequency energy. Europace 2011; 13(1):37-44.

20. Haeusler KG, Koch L, Herm J, Kopp UA, Heuschmann PU, Endres M, Schultheiss HP, Schirdewan A, Fiebach JB. 3 Tesla MRI- Detected Brain Lesions after Pulmonary Vein Isolation for Atrial Fibrillation: Results of the MACPAF Study. J Cardiovasc Electrophysiol 2012 Jul 25. DOI: 10.1111/j.1540-8167.2012.02420.x.
21. Deneke T, Shin DI, Balta O, Bünz K, Fassbender F, Mügge A, Anders H, Horlitz M, Päsler M, Karthikapallil S, Arentz T, Beyer D, Bansmann M. Postablation asymptomatic cerebral lesions: Long-term follow-up using magnetic resonance imaging. Heart Rhythm 2011; 8:1705–11.
22. Schwarz N, Kuniss M, Nedelmann M, Kaps M, Bachmann G, Neumann T, Pitschner HF, Gerriets T. Neuropsychological decline after catheter ablation of atrial fibrillation. Heart Rhythm. 2010 Dec;7(12):1761-7.
23. Ringer TM, Neumann-Haefelin T, Sobel RA, Moseley ME, Yenari MA. Reversal of early diffusion-weighted magnetic resonance imaging abnormalities does not necessarily reflect tissue salvage in experimental cerebral ischemia. Stroke 2001; 32:2362-9
24. Feinberg WM, Seeger JF, Carmody RF, Anderson DC, Hart RG, Pearce LA. Epidemiologic features of asymptomatic cerebral infarction in patients with nonvalvular atrial fibrillation. Arch Intern Med. 1990;150:2340-4.
25. Ezekowitz MD, James KE, Nazarian SM, Davenport J, Broderick JP, Gupta SR, Thadani V, Meyer ML, Bridgers SL. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Circulation. 1995;92:2178-2182.
26. EAFT Study Group. European Atrial Fibrillation Trial. Silent brain infarction in nonrheumatic atrial fibrillation. Neurology. 1996;46:159-65

27. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864-2870.

28. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263–72.

29. Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. Journal of clinical and experimental neuropsychology 1998;20(3):310–9.

30. Kwee RM, Kwee TC. Virchow-Robin Spaces at MR Imaging. Radiographics 2007; 27:1071-86.

31. Pantoni L, Garcia JH. Pathogenesis of Leukoaraiosis. A review. Stroke 1997; 28:652-659.

32. Pianelli M, Scaglione M, Anselmino M, Caponi D, Garcia P, Cesarani F, Toso E, Raimondo C, Halimi F, Leclercq JF, Gaita F. Delaying cardioversion following 4-week anticoagulation in case of persistent atrial fibrillation after a transcatheter ablation procedure to reduce silent cerebral thromboembolism: a single-center pilot study. J Cardiovasc Med. 2011 Nov;12(11):785-9.

33. Scaglione M, Blandino A, Raimondo C, Caponi D, Di Donna P, Toso E, Ebrille E, Cesarani F, Ferrarese E, Gaita F. Impact of ablation catheter irrigation design on silent cerebral embolism after radiofrequency catheter ablation of atrial fibrillation: results from a pilot study. J Cardiovasc Electrophysiol. 2012 Aug;23(8):801-5. Epub 2012 Apr 11.

34. Anfinsen OG, Gjesdal K, Brosstad F, et al. The activation of platelet function, coagulation, and fibrinolysis during catheter radiofrequency ablation in heparinized patients. J Cardiovasc Electrophysiol 1999;10:503–512.

35. Lee DS, Dorian P, Downar E, et al. Thrombogenicity of radiofrequency ablation procedures: what factors influence thrombin generation? Europace 2001; 3:195–200.
36. Wood MA, Shaffer KM, Ellenbogen AL, Ownby ED. Microbubbles during radiofrequency catheter ablation: composition and formation. Heart Rhythm 2005; 2:397–403.
37. Neumann T, Kuniss M, Conradi G et al. MEDAFI-Trial (Micro-embolization during ablation of atrial fibrillation): comparison of pulmonary vein isolation using cryoballoon technique vs. radiofrequency energy. Europace 2011; 13(1):37-44.
38. Haeusler KG, Koch L, Herm J et al. 3 Tesla MRI- Detected Brain Lesions after Pulmonary Vein Isolation for Atrial Fibrillation: Results of the MACPAF Study. J Cardiovasc Electrophysiol 2012.
39. Bunch TJ, Crandall BG, Weiss JP et al. Patients Treated with Catheter Ablation for Atrial Fibrillation Have Long-Term Rates of Death, Stroke, and Dementia Similar to Patients Without Atrial Fibrillation. J Cardiovasc Electrophysiol 2011; 22:839-45.
40. Medi C, Evered L, Silbert B et al. Subtle Post-Procedural Cognitive Dysfunction After Atrial Fibrillation Ablation. J Am Coll Cardiol 2013;62:531–9.