# Silent Cerebral Embolism during Atrial Fibrillation Ablation: Pathophysiology, Prevention and Management

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**Abstract**

Although many efforts have been directed to improve atrial fibrillation transcatheter ablation safety, thromboembolism to the brain remains one of the major complications. In fact several studies have confirmed occurrence of silent cerebral embolic lesions by post-procedure magnetic resonance imaging, the present review will focus on the possible mechanisms leading to silent cerebral embolism in an attempt to provide recommendations holding the potential to reduce the incidence of this clinically relevant complication.

## Introduction

Transcatheter ablation of atrial fibrillation (AF) is a well-established treatment for symptomatic patients refractory to antiarrhythmic drugs, aiming to restore sinus rhythm, improve AF related symptoms and prevent AF related complications. Efficacy of transcatheter AF ablation is satisfactory in experienced centers, and, according to present data, is considered superior to any antiarrhythmic drug.[1,2]

Many efforts have been made over the past years to improve safety of catheter AF ablation. As an invasive procedure, it carries a risk of local and systemic complications, the most harmful being cardiac tamponade and stroke. Despite the introduction of new catheters, energy sources, new imaging and navigation tools,[3] the risks deriving from the procedure have not been cancelled, and cerebrovascular accidents remain in fact one of the most feared and frequent complications, ranging from 0.5 to 1.0%.[4]

Besides symptomatic cerebral events, AF ablation also carries a risk of silent cerebral embolic lesions. Performing cerebral magnetic resonance imaging (MRI) before and after catheter ablation, Lickfett et al. first reported in a small group of patients the detection of new silent cerebral ischemias (SCI),[5] and this was subsequently confirmed by our group in a larger population of patients.[6] Given that SCI, frequently found in patients with carotid disease, hypertensive cerebrovascular disease or AF, relate to neurocognitive impairment

and dementia[7,8,9,10,11,12] silent cerebral embolism following transcatheter ablation warrants careful consideration.

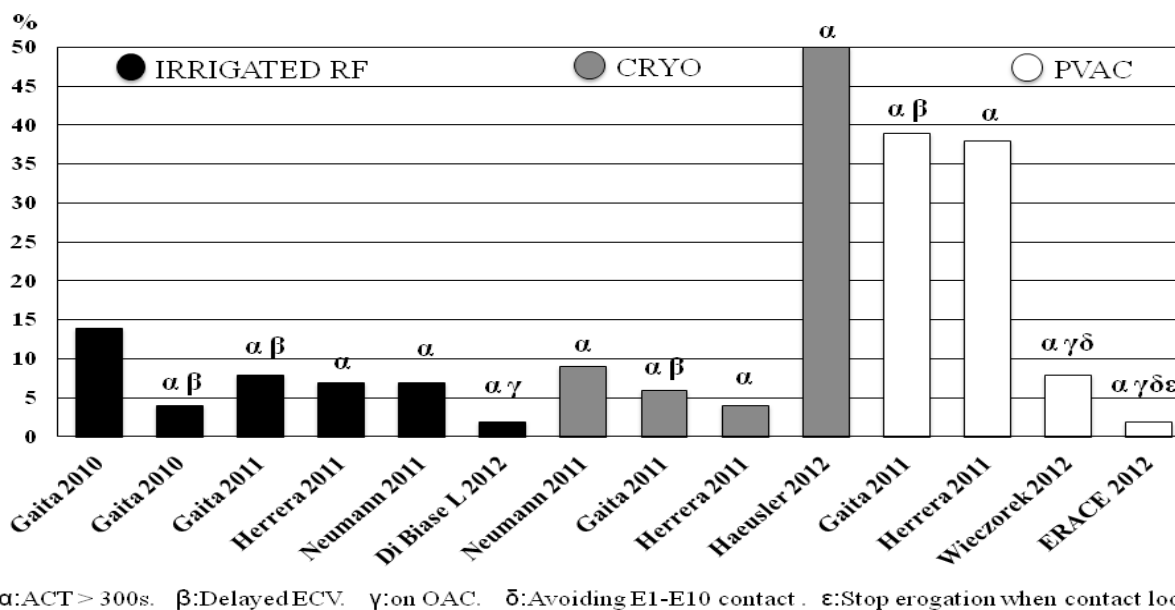## Pathophysiology of Silent Embolic Lesions

The origin of SCI during transcatheter ablation is mainly consequent to three mechanisms: clot formation, char formation and air/gas embolism. Any foreign body introduced in the blood pool bing potentially thrombogenic, clot formation may be expected on ablation and mapping catheters and sheaths. Char formation may instead be induced by the energy source on the tissue. Eventually air embolism may derive from catheters insertion and mobilization, but also from radiofrequency (RF) induced high temperatures producing intravascular gas bubbles.

Introduction of any foreign body into the blood pool stimulates clot formation.[13,14] The 2012 ESC Consensus on AF ablation recommends to maintain an activated clotting time (ACT) between 300 and 400 seconds during the procedure, to limit both thrombotic and hemorrhagic complications.[15] In fact, a study by Ren et al. reported a lower incidence of spontaneous echo contrast and thrombi in the left atrium, detected by intracardiac echocardiography when ACT was maintained over 300 seconds during the procedure.[16] This confirms that a stronger heparinization during the procedure may be helpful to avoid thromboembolic complications. Furthermore, transseptal puncture performed to reach left atrium and pulmonary veins when a patent foramen ovale is not present, causes platelet activation.[17] requiring administration of a bolus of heparin before this procedural step.[15]

Char formation is indeed intrinsic to ablation techniques and energy sources used during the procedure. The most frequently used energy source is Radiofrequency (RF). RF produces thermal damage to the atrial tissue and is responsible of electrical conduction

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α:ACT > 300s.    β:Delayed ECV.    γ:on OAC.    δ:Avoiding E1-E10 contact .    ε:Stop erogation when contact loose

**Figure 1:** Incidence of silent cerebral ischemias according to different ablation tools and procedural strategies introduced to reduce silent embolism burden.

RF: radiofrequency. CRYO: cryoenergy. PVAC: pulmonary vein ablation catheter. ACT: activated clotting time. ECV: electrical cardioversion. OAC: oral anticoagulation. E1-E10: electrode1-electrode10.

block, isolation of triggers and interruption of circuits underlying AF initiation and maintenance. On the flip side it may become potentially harmful, causing endothelial layer damage and coagulation cascade activation, eventually leading to thrombus formation.[18,19] Ablation catheters, despite been studied and designed to reduce the electrode-endothelium interface temperature, thermal thrombus and char formation at the catheter tip remains one of the mechanisms responsible of the thromboembolic risk.[20]

Char formation is related to heat-induced denaturization of blood proteins, and can occur despite high levels of anticoagulation. In this setting, the introduction of open-irrigated catheters permitted a more efficient heat control achieving reduced thrombus formation in animal models.[21] These catheters are, characterized by a continuous saline irrigation, which allows a prompt and effective heat dispersion, ensure interface temperature reduction, obviating tissue overheating.

Eventually, alternative energy sources, in particular cryoenergy, have been proposed. Cryoenergy reported lower platelet and fibrin activation,[17] leading to lower incidence of thrombus formation in vitro, by preserving the endothelial layer during ablation[22]; results are however contradictory, recent studies reported similar levels of platelet activity and coagulation activation by cryoenergy and RF.[23]

The third mechanism of cerebrovascular damage is air/gas embolism. Gas microbubble formation has been demonstrated during experimental models treated by elevated temperatures, with two different patterns[24]: type 1, or scattered microbubbles, with a concentration <1 μl per minute of ablation, reflecting early tissue overheating; and type 2, or continuous microbubbles, with a concentration >1 μl per minute of ablation, reflecting important impedance rise during RF delivery. The pattern of microbubbles is predicted by tissue-electrode interface temperature, and not by RF power or catheter tip temperature.[25,26] The direct visualization of these microbubbles by intracardiac echocardiography has been suggested to improve ablation safety and reduce endothelial damage by guiding energy titration.[24] Although microbubbles have been related to

microembolic signals at transcranial Doppler[27] and cerebral lesions following embolization of air microbubbles have been described using cerebral MRI in animal studies,[28] the clinical impact in humans remains uncertain.

In the meantime, considering energy sources used for ablation, by transcranial Doppler, Sauren et al. have demonstrated a lower incidence of microembolic signals during catheter AF ablation using cryoballoon or irrigated RF catheters compared to conventional RF catheters.[29]

Finally, air embolism may be related to the introduction of ablation devices.[30,31] Careful catheter handling, avoidance of multiple catheter exchanges and continuous heparin flushing may therefore be useful in reducing the risk of SCI.

### Current Literature on Silent Cerebral Ischemias Following Transcatheter Atrial Fibrillation Ablation

Evidence on the incidence of SCI following AF transcatheter ablation is summarized in Table 1. The first study detecting asymptomatic cerebral embolism at MRI scan following AF catheter ablation by open-irrigated RF catheter reported a 10% incidence of new SCI in a small population of 20 patients.[5]

Shortly after our group performed a study on 232 patients reporting a 14% incidence of SCI following AF ablation.[6] In this study the ACT value maintained during the procedure strongly related to the incidence of SCI: 9% of patients with an ACT > 250 reported SCI following the procedure compared to 17% within those maintaining lower ACT values. Another parameter independently related to SCI incidence following the procedure was electric or pharmacological cardioversion in case of persistent AF at the end of procedure. Clinical parameters such as age, hypertension, diabetes mellitus, previous history of stroke, type of AF, and pre-ablation antithrombotic treatment did not relate to incidence of SCI.

Another study by Schrinkel et al., performing cerebral MRI before and after AF ablation by irrigated RF catheter in 53 patients with
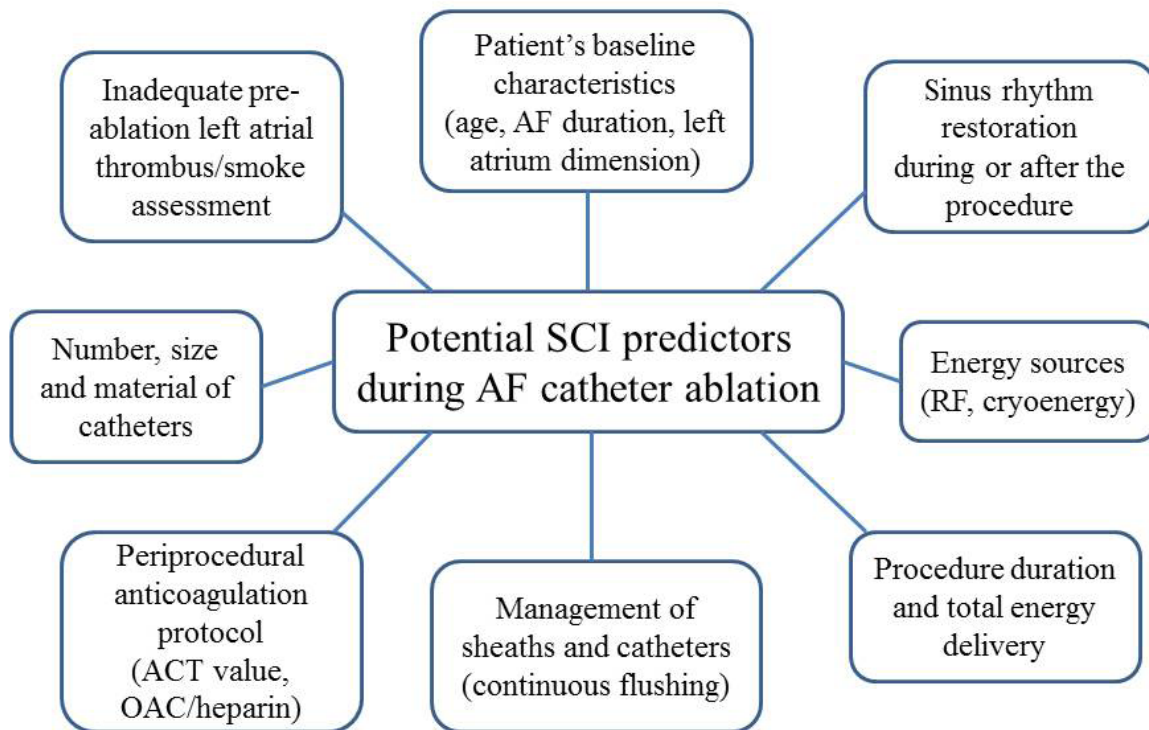
**Figure 2:**    Variables playing a potential role in the incidence of silent cerebral ischemias following transcatheter atrial fibrillation ablation.

SCI: silent cerebral ischemias. AF: atrial fibrillation. RF: radiofrequency. ACT: activated clotting time. OAC: oral anticoagulation.

paroxysmal AF, confirmed an 11% incidence of SCI. Concomitant coronary artery disease, left ventricular dilatation and left ventricular hypertrophy emerged as predictors of this complication.[34] On the other side higher incidence of SCI was reported by Deneke et al. enrolling 86 patients undergoing AF ablation by irrigated RF catheter. In this dataset a 38% incidence of SCI at cerebral MRI was recorded after the procedure.[35] In this case previous cerebral lesions at MRI and the duration of RF delivery related to SCI incidence.

Following these first reports, different protocols and ablation tools have been tested to reduce the incidence of SCI. A pilot study has been performed delaying electrical cardioversion after 4 weeks of oral anticoagulation (OAC) with INR 2.0-3.0 in patients with persistent AF at the end of the ablation procedure. All the patients underwent cerebral MRI the day before, the day after the ablation, and following sinus rhythm restoration (spontaneous or by electrical cardioversion). Among the total population of 95 patients, none in which electrical cardioversion was performed after the planned 4 weeks of OAC since sinus rhythm had not spontaneously been restored reported new SCI at the MRI scan.[36]

Furthermore a multicenter study underlined the safety of performing ablation under therapeutic OAC, reporting lower symptomatic thromboembolic complications compared with ablation under heparin, without an excessive bleeding risk46. A small preliminary experience on 51 patients undergoing AF ablation under uninterrupted OAC plus heparin during the procedure, maintaining ACT above 300 seconds, reported encouraging results also concerning silent events with only one patient (2%) positive for new SCI at post-procedural cerebral MRI.[38] However in a larger study Martinek et al. performed ablation by irrigated RF catheters under

uninterrupted OAC in 131 consecutive patients. After the procedure, they unexpectedly found a 12.2% incidence of new SCI at cerebral MRI,[39] not different from that reported among patients undergoing heparin bridging, highlighting the fact that clot formation is not the sole thromboembolic mechanism.[47] In this dataset age, spontaneous echo contrast in the left atrium, complex fractionated atrial electrograms (CFAE) ablation and intraprocedural electrical cardioversion emerged as SCI predictors.

Ablation tools and energy sources have impact on SCI incidence. The pulmonary vein ablation catheter (PVAC) is a duty-cycle phased RF ablation catheter ensuring rapid and simple procedures thanks to its ability both to map and ablate. The preset energy settings allow to deliver simultaneously unipolar and bipolar current with an erogated/not erogated ratio of 10-90% over time, a temperature target of 60° C and a low power output, which enables lesion depth control, reporting promising safety and outcome results accompanied by reduction in fluoroscopy and procedural times.[48,49,50] Surprisingly, in a study enrolling 183 patients to compare the incidence of SCI by PVAC, irrigated RF and cryoballoon, the PVAC technology reported an unsuspected higher, 38.9%, incidence of SCI compared to 8.3% by RF and 5.6% by cryoenergy41. Similar results have subsequently been confirmed by another multicenter study.[42]

In order to explain this SCI excess by PVAC, an animal model has been designed allowing the detection of gas and solid particles during catheter introduction, withdrawal, manipulation, and energy delivery51. Type 1 (<1 µl per minute of ablation) gas bubbles during PVAC ablation resulted more common during bipolar ablation than in unipolar mode, while type 2 (>1 µl per minute of ablation) gas bubble production was high when electrodes 1 and 10 were in close

proximity; eventually a significant amount of air bubbles was recorded during PVAC catheter exchanges. Following these experiments, the manufacturer recommended the following amendments to reduce the embolic risk during ablation by PVAC: deactivate electrode pairs not maintaining good contact with the pulmonary veins during ablation (recognized by the relationship between power and temperature on the multi-channel generator); ensure that electrodes 1 and 10 of the PVAC catheter are separated; reduce air entrance by an underwater submerged introduction/exchange technique.

According to these recommendations, a multicenter study, the ERACE study [Evaluate Reduction of Asymptomatic Cerebral Embolism], was designed enrolling 60 patients for AF ablation by PVAC. The procedure was also performed under continuous anticoagulation (INR > 2) and with a procedural ACT target of 350 seconds. The results, not yet published, have recently been presented by the manufacturer reporting a very low incidence of post-ablation

| Table :1 | | Landmark studies on new oral anticoagulants in stroke prevention in atrial fibrillation | | | | | |
|---|---|---|---|---|---|---|---|
| Author, year (ref) | Pts | MRI timing | Anticoagulation protocol | Source of energy | SCI incidence | SCI predictors | Lesion follow-up |
| Lickfett, 2006 (5) | 20 | 1 day pre 1 day post | Heparin, ACT >250s | Irrigated RF | 10.0% | - | - |
| Gaita, 2010 (6) | 232 | 1 day pre 1 day post | Heparin, ACT >250s | Irrigated RF | 14.0% | Cardioversion ACT<250sec | - |
| Schwarz,2010( ) | 23 | 1 day pre 1 day post | Heparin, ACT > 300 | Irrigated RF | 14.3% | - | 3 months: verbal memory impairment |
| Schrickel,2010( ) | 53 | 1 day pre 1 day post | Heparin, ACT >250s | Irrigated RF | 11.0% | CAD, LV Hypertrophy LV dilatation | |
| Deneke, 2011 ( ) | 86 | 1 day pre 1 day post | Heparin, ACT > 300 | Irrigated RF | 38.0% | Preablation SCI | 6 months: 94% regression, no cognitive impairment |
| Pianelli, 2011 ( ) | 95 | 1 day pre 1 day post 1 month | Heparin, ACT >250s | Irrigated RF | 6.0% | Cardioversion | SCI from 38 to 13% if cardioversion postponed 4 weeks post-ablation |
| Scaglione, 2012 ( ) | 85 | 1 day pre | Heparin, ACT > 300s | Irrigated RF, Super irrigated RF | 7.5% 5.0% | ACT <320sec | - |
| Di Biase, 2011 ( ) | 51 | 1 day pre 1 day post | OAC, ACT > 300s | rrilgated RF | 2.0% | - | - |
| Martinek, 2013 ( ) | 131 | 1 day pre 1 day post | OAC, ACT > 300s | Irrigated RF | 12.2% | Age Echocontrast CFAE ablation Cardioversion | - |
| Ichiki, | 100 | 1 day pre 1 day post | Heparin, ACT > 250s | Irrigated RF: CFAE Irrigated RF: CFAE + PVI | 12.2% 7.3% | 25.78 | |
| Gaita, 2011 ( ) | 108 | 1 day pre 1 day post | Heparin, ACT > 300 | Irrigated RF Cryoballoon PVAC | 8.3% 5.6% 38.9% | PVAC | - |
| Herrera Siklody, 2011 ( ) | 74 | 1 day pre 1 day post | Heparin, ACT > 300 | Irrigated RF Cryoballoon PVAC | 7.4% 4.3% 37.5% | PVAC | - |
| Neumann, 2011 ( ) | 89 | 1 day pre 1 day post | Heparin, ACT > 300s | Irrigated RF Cryoballoon | 6.8% 8.9% | Age | 3 months: 100% regression |
| Haeusler, 2013 ( ) | 37 | 1 day pre 1 day post | Heparin, ACT > 300s | RF Mesh Ablator Cryoballoon | 27.0% 50.0% | Low EF AF episode | 6 months: 82% regression, no cognitive impairment |
| Wieczorek, 2013 ( ) | 37 | 1 day pre 1 day post | OAC, ACT > 300s | PVAC | 37.0% | E1-E10 contact | 1 month: 90% regression |
| ERACE, 2013? ( ) | 60 | 1 day pre 1 day post | OAC, ACT > 350s | PVAC | 1.7% | - | 1 month: 100% regression |

SCI, only 1.7%,[46] rendering very attractive this type of catheter when correctly used.

Interesting reports have also been published concerning cryoablation. Neumann et al. compared the incidence of SCI by cryoablation and RF ablation in the MEDAFI trial [Micro-Embolization During Ablation of Atrial fibrillation], which enrolled 89 patients who underwent AF ablation either with cryoballoon or irrigated RF catheters. At post-procedure MRI incidence of SCI was 7.9%, without statistical difference between the two ablation strategies.[43] The only parameter found in this study to be related to the incidence of new SCI was age.

On the other side the MACPAF study [Mesh Ablator versus Cryoballoon Pulmonary Vein Ablation of Symptomatic Paroxysmal Atrial Fibrillation], a trial comparing ablation efficacy and safety by cryoballoon and a balloon-like catheter delivering RF reported contradictory results.[52] An analysis of these patients, including cerebral MRI before and after the procedure, reported a 41% incidence of new SCI at the 3 Tesla MRI scan in the 37 patients enrolled. In particular, cryoenergy did not show a reduction in SCI incidence compared with RF balloon, and no significant predictor was found,[44] apart from a trend towards significance for reduced left ventricular ejection fraction.

In summary, the incidence of SCI following AF catheter ablation is a relatively frequent complication, even if predictors of SCI are not yet completely categorized.[47,53,54,55] The contradictory results among different studies most probably reflect the variety of procedural AF ablation techniques, protocols, operators experience, patients selection and also cerebral MRI protocols (1.5 Tesla / 3 Tesla MRI).[56] As the decreasing incidence rates over time (Figure 1) testimonies, acknowledgement of this complication, however, has clearly introduced beneficial effects.

## Silent Cerebral Ischemias Follow-Up and Potential Preventive Measures

SCI have been related to a greater incidence of dementia and neurological impairment.[57] Despite this, at present, only few studies investigated the relationship between post-ablation SCI and dementia or neurocognitive decline (Table 1). Even if Bunch et al. reported in their large study a lower incidence of cerebrovascular events and dementia among AF patients undergoing RF ablation compared with AF patients not treated with ablation,[58] the recent findings at post-ablation MRI call for attention towards a potential ablation related neurological risk.

Considering post-ablation SCI, Schwarz et al. reported at three-months follow-up after catheter ablation a significant impairment concerning verbal memory, without alterations in the other neuropsychological parameters examined.[33] However this decline seemed not related to the incidence of new SCI.

Another study reporting SCI follow-up is the work by Deneke et al. which showed no sign of neurological impairment at clinical examination in these patients, and reported that the vast majority (94%) of SCI detected at post-ablation MRI reduced their diameter and eventually disappeared at three-months follow-up;[35] in particular those less than 10 mm in diameter were not further recognizable during follow-up. Similar follow-up results have been reported in the MEDAFI trial,[43] in which no lesion was visible at three-months follow-up cerebral MRI. Also the MACPAF study reported similar results, with 82% of the new post-ablation SCI

disappearing at six-months follow-up,[44] confirming also the absence of neuropsychological decline with neurocognitive tests results unchanged during follow-up. Eventually, the study by Wieczorek et al. reported complete regression of 90% of the SCI detected after the ablation at one-month follow-up.[45] Consistently, no neurological symptom or alteration was found in patients with positive MRI.

According to these data, there is evidence that SCI disappear or at least reduce themselves under the spatial resolution power of the cerebral MRI over time, without evident acute neurological or cognitive implications. However, since it is not surely defined if SCI regression relates to complete neuronal recovery, excluding long-term neurological and cognitive impairment, physicians need to be aware of AF ablation related SCI. Considering the significant amount of patients needing one or more additional ablation procedures to achieve rhythm control, the potential impact of silent lesions warrants attention.

Based on the afore reported literature and our personal experience on this topic rich of unresolved issues, the following considerations emerge to address and correct potential predictors of SCI (Figure 2). Patient selection plays a relevant role, age being one of the recurrent risk factors. Moreover, selection of patients with paroxysmal AF, small left atrial volume and short arrhythmia duration may help to reduce SCI incidence. Other baseline characteristics, such as reduced left ventricular ejection fraction, left ventricular hypertrophy and concomitant coronary artery disease need to be further tested. Considering procedural characteristics, awaiting further clinical evidences, in case of persistent AF after ablation, delaying electrical cardioversion to after one month of therapeutic OAC might play a role in reducing SCI occurrence. In addition total energy delivery and procedural duration have been reported to predict SCI incidence. The smaller number of catheters used, the minor number of exchanges, the most careful device insertion (under saline submerged technique) and sheath management together with long sheath withdrawal into the right atrium after transseptal puncture are likely related to a reduction in SCI consequent to air embolism. Eventually, cerebral MRI needs to be standardized to permit homogenous comparisons within patients, ablation tools and techniques.[32]

## Conclusions:

In conclusion additional data are needed to comprehensively describe the precise genesis and clearly identify correctable predictors of SCI to definitely improve AF transcatheter ablation safety.

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